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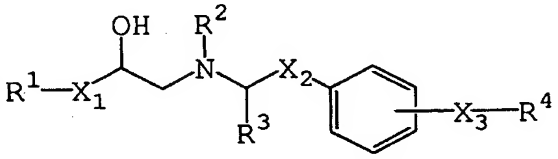
(54) Title: NEW AMINOALCOHOL DERIVATIVES



[I]

(57) Abstract: The present invention relates to a compound of formula [I]: wherein X_1 is bond or $-OCH_2-$; X_2 is $-(CH_2)_n-$, in which n is 1 or 2; X_3 is bond, -O- or -NH-; R^1 is phenyl, indolyl or carbazolyl, each of which is optionally substituted with one or two substituent(s) selected from the group consisting of hydroxy, halogen, nitro, amino, formyl, (lower)alkylsulfonylamino, aryl(lower)alkoxy and hydroxy(lower)alkyl; R^2 is hydrogen or aryl(lower)alkyl; R^3 is hydrogen or hydroxy(lower)alkyl; R^4 is aryl, 4-quinolyl, phthalazinyl, quinazolinyl, cinnolinyl or naphthyridinyl, each of which is optionally substituted with one or two substituent(s) defined in the specification, or a salt thereof. The compound [I] of the present invention and pharmaceutically acceptable salts thereof are useful for the prophylactic and/or the therapeutic treatment of pollakiurea or urinary incontinence.

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DESCRIPTION

NEW AMINOALCOHOL DERIVATIVES

TECHNICAL FIELD

This invention relates to new aminoalcohol derivatives and salts thereof which are useful as a medicament.

DISCLOSURE OF INVENTION

This invention relates to new aminoalcohol derivatives and salts thereof.

More particularly, it relates to new aminoalcohol derivatives and salts thereof which act as selective β_3 adrenergic receptor agonists and therefore have gut sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence and anti-pollakiuria activities, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to a method of using the same therapeutically in the treatment and/or prevention of gastro-intestinal disorders caused by smooth muscle contractions in human beings or animals, and more particularly for the treatment and/or prevention of spasm or hyperanakinesia in case of irritable bowel syndrome, gastritis, gastric ulcer, duodenal ulcer, enteritis, cholecystopathy, cholangitis, urinary calculus, and the like; for the treatment and/or prevention of ulcer such as gastric ulcer, duodenal ulcer, peptic ulcer, ulcer caused by non steroidal anti-inflammatory drugs, and the like; for the treatment and/or prevention of dysuria such as pollakiuria, urinary incontinence, and the like in case of nervous pollakiuria, neurogenic bladder dysfunction, nocturia, unstable bladder, cystospasm, chronic cystitis, chronic prostatitis, prostatic hypertrophy, and the like; for the treatment and/or prevention

of pancreatitis, obesity, diabetes, glycosuria, hyperlipidemia, hypertension, atherosclerosis, glaucoma, melancholia, depression, and the like, and for the treatment and/or prevention of diseases as the result of insulin resistance (e.g. hypertension, hyperinsulinemia, etc.); for the treatment and/or prevention of neurogenetic inflammation; and for reducing a wasting condition, and the like; for the treatment and/or prevention of conditions such as hyper-triglyceridaemia, hypercholesterolaemia and in lowering high density lipoprotein levels as well as in the treatment of atherosclerotic and cardiovascular diseases and related conditions; for inhibiting uterine contractions, preventing premature labor, and treating and preventing dysmenorrhea.

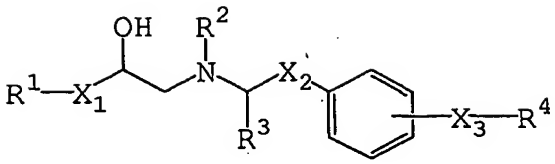
One object of this invention is to provide new and useful aminoalcohol derivatives and salts thereof which have gut sympathomimetic, anti-ulcerous, lipolytic, anti-urinary incontinence and anti-pollakiuria activities.

Another object of this invention is to provide processes for the preparation of said aminoalcohol derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said aminoalcohol derivatives and salts thereof.

Still further object of this invention is to provide a therapeutical method for the treatment and/or prevention of aforesaid diseases in human beings or animals, using said aminoalcohol derivatives and salts thereof.

The object aminoalcohol derivatives of this invention are new and can be represented by the following general formula [I]:



[I]

wherein

X_1 is bond or $-OCH_2-$;

X_2 is $-(CH_2)_n-$, in which n is 1 or 2;

X_3 is bond, -O- or -NH-;

R^1 is phenyl, indolyl or carbazolyl, each of which is optionally substituted with one or two substituent(s) selected from the group consisting of hydroxy, halogen, nitro, amino, formyl, (lower)alkylsulfonylamino, aryl(lower)alkoxy and hydroxy(lower)alkyl;

R^2 is hydrogen or aryl(lower)alkyl;

R^3 is hydrogen or hydroxy(lower)alkyl;

R^4 is aryl, 4-quinolyl, phthalazinyl, quinazolinyl, cinnolinyl or naphthyridinyl, each of which is optionally substituted with one or two substituent(s) selected from the group consisting of fluoro, carboxy, nitro, amino, halo(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxycarbonyl, (lower)alkylsulfonylcarbamoyl optionally substituted with cyclo(lower)alkyl or halogen atom(s) in which amine hydrogen is optionally substituted with lower alkyl,
cyclo(lower)alkylsulfonylcarbamoyl,
arylsulfonylcarbamoyl,
(lower)alkylcarbonylamino in which amine hydrogen is optionally substituted with lower alkyl,
lower alkoxy optionally substituted with carboxy or (lower)alkoxycarbonyl,
(lower)alkylsulfonylamino in which amine hydrogen is optionally substituted with lower alkyl,

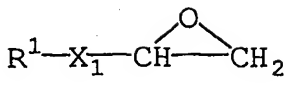
ureido in which amine hydrogen(s) is(are) optionally substituted with lower alkyl,
(lower)alkoxycarbonylamino in which amine hydrogen is optionally substituted with lower alkyl, and

$-CONR^5R^6$

(wherein R^5 and R^6 are independently hydrogen or lower alkyl optionally substituted with hydroxy, carboxy, lower alkoxy, (lower)alkoxycarbonyl or halogen atom(s), or R^5 and R^6 together can be four or five methylene groups, of which one methylene group can be replaced by O, N-H or N-(lower)alkyl), and a salt thereof,
provided that
(1) when R^4 is unsubstituted 4-quinolyl, X_2 is $-(CH_2)_2-$,
(2) when R^4 is 4-quinolyl substituted with one substituent which is ethoxycarbonyl, carboxy, carbamoyl or methoxy substituted at the 7-position thereof, X_1 is a bond,
(3) when R^4 is 4-quinolyl substituted with fluorine, it is substituted at the 2-, 3-, 5-, 7- or 8-position thereof,
(4) when R^4 is aryl optionally substituted with halogen, X_3 is bond or -NH-, and
(5) when R^4 is naphthyridinyl, it is substituted with the above-mentioned one or two substituent(s).

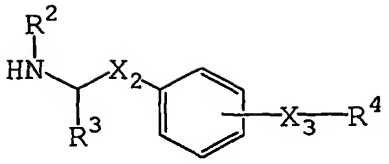
The object compound [I] or a salt thereof can be prepared by the following processes.

Process 1

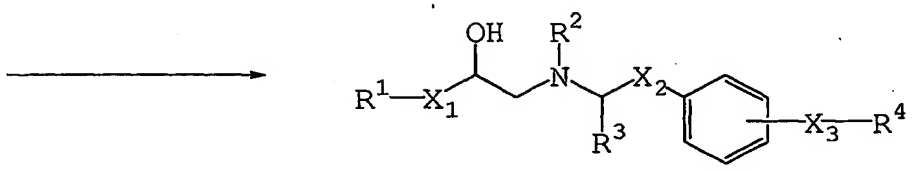


[II]
or a salt thereof

+

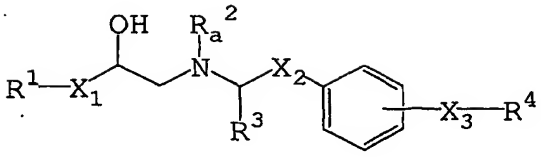


[III]
or a salt thereof



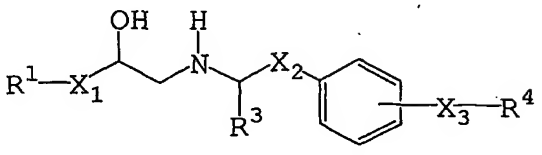
[I]
or a salt thereof

Process 2



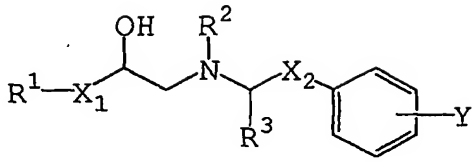
[Ia]
or a salt thereof

elimination reaction
of amino protective group



[Ib]
or a salt thereof

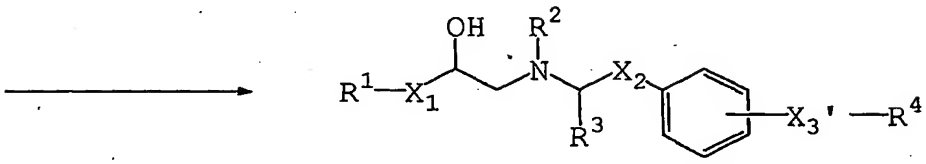
Process 3



[IV]
or a salt thereof

+

[V]
or a salt thereof



[Ic]
or a salt thereof

wherein X_1, X_2, X_3, R^1, R^2, R^3 and R^4 are each as defined above,

X_3' is -O- or -NH-,

Y is hydroxy or amino,

R_a^2 is amino protective group, and

X is halogen.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl" moiety in the terms of "(lower)alkylsulfonylamino", "hydroxy(lower)alkyl", etc. may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, neopentyl, hexyl, isohexyl, and the like, preferably one having 1 to 4 carbon atom(s).

Suitable "lower alkoxy" and "lower alkoxy" moiety in the terms of "(lower)alkoxycarbonyl", etc. may include straight or branched one such as methoxy, ethoxy, propoxy, isopropoxy, 1-ethylpropoxy, butoxy, sec-butoxy, tert-butoxy, pentyloxy, isopentyloxy, neopentyloxy, tert-pentyloxy, hexyloxy, isohexyloxy, and the like, preferably methoxy, ethoxy, propoxy and isopropoxy, and more preferably methoxy.

Suitable "cyclo(lower)alkyl" and "cyclo(lower)alkyl" moiety in the terms of "cyclo(lower)alkylsulfonylcarbamoyl", etc. may include cycloalkyl having 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, and the like, preferably one having 3 to 4 carbon atoms.

Suitable "aryl" and "aryl" moiety in the terms of "aryl(lower)alkyl", "arylsulfonylcarbamoyl", etc. may include phenyl, naphthyl, anthryl, and the like, preferably phenyl.

Suitable "halogen" and "halogen" moiety in the term of "halo(lower)alkyl" may include fluoro, chloro, bromo, iodo, and the like, preferably fluoro and chloro.

Suitable halo(lower)alkyl may include fluoro(lower)alkyl [e.g. fluoromethyl (e.g. monofluoromethyl, difluoromethyl, trifluoromethyl), fluoroethyl, fluoropropyl, fluorobutyl, fluoropentyl, fluorohexyl, and the like], chloro(lower)alkyl [e.g. chloromethyl (e.g. monochloromethyl, dichloromethyl, trichloromethyl), chloroethyl, chloropropyl, chlorobutyl, chloropentyl, chlorohexyl, and the like], bromo(lower)alkyl, iodo(lower)alkyl, chlorofluoro(lower)alkyl (e.g. monochlorodifluoromethyl, dichloromonofluoromethyl, and the like), and the like, preferably trifluoromethyl.

Suitable hydroxy(lower)alkyl may include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, and the like, preferably hydroxymethyl.

Suitable (lower)alkylcarbonylamino may include N-acetylamino, N-(ethylcarbonyl)amino, N-(propylcarbonyl)amino, N-(butylcarbonyl)amino, N-(pentylcarbonyl)amino, N-(hexylcarbonyl)amino, and the like, preferably N-acetylamino.

Suitable (lower)alkylcarbonylamino in which amine hydrogen substituted with lower alkyl may include N-methyl-N-acetylamino, N-methyl-N-(ethylcarbonyl)amino, N-methyl-N-(propylcarbonyl)amino, N-methyl-N-(butylcarbonyl)amino, N-methyl-N-(pentylcarbonyl)amino, N-methyl-N-(hexylcarbonyl)amino, N-ethyl-N-acetylamino, N-ethyl-N-(ethylcarbonyl)amino, N-ethyl-N-(propylcarbonyl)amino, N-ethyl-N-(butylcarbonyl)amino, N-ethyl-N-(pentylcarbonyl)amino, N-ethyl-N-(hexylcarbonyl)amino, N-propyl-N-acetylamino, N-propyl-N-(ethylcarbonyl)amino, N-propyl-N-(propylcarbonyl)amino, N-propyl-N-(butylcarbonyl)amino, N-propyl-N-(pentylcarbonyl)amino, N-propyl-N-

(hexylcarbonyl)amino, N-butyl-N-acetylamino, N-butyl-N-(ethylcarbonyl)amino, N-butyl-N-(propylcarbonyl)amino, N-butyl-N-(butylcarbonyl)amino, N-butyl-N-(pentylcarbonyl)amino, N-butyl-N-(hexylcarbonyl)amino, N-pentyl-N-acetylamino, N-pentyl-N-(ethylcarbonyl)amino, N-pentyl-N-(propylcarbonyl)amino, N-pentyl-N-(butylcarbonyl)amino, N-pentyl-N-(pentylcarbonyl)amino, N-pentyl-N-(hexylcarbonyl)amino, N-hexyl-N-acetylamino, N-hexyl-N-(ethylcarbonyl)amino, N-hexyl-N-(propylcarbonyl)amino, N-hexyl-N-(butylcarbonyl)amino, N-hexyl-N-(pentylcarbonyl)amino, N-hexyl-N-(hexylcarbonyl)amino, and the like, preferably N-methyl-N-acetylamino.

Suitable (lower)alkylsulfonylamino may include N-(methanesulfonyl)amino, N-(ethylsulfonyl)amino, N-(propylsulfonyl)amino, N-(butylsulfonyl)amino, N-(pentylsulfonyl)amino, N-(hexylsulfonyl)amino, and the like, preferably N-(methanesulfonyl)amino.

Suitable (lower)alkylsulfonylamino in which amine hydrogen is substituted with lower alkyl may include N-methyl-N-(methanesulfonyl)amino, N-methyl-N-(ethylsulfonyl)amino, N-methyl-N-(propylsulfonyl)amino, N-methyl-N-(butylsulfonyl)amino, N-methyl-N-(pentylsulfonyl)amino, N-methyl-N-(hexylsulfonyl)amino, N-ethyl-N-(methanesulfonyl)amino, N-ethyl-N-(ethylsulfonyl)amino, N-ethyl-N-(propylsulfonyl)amino, N-ethyl-N-(butylsulfonyl)amino, N-ethyl-N-(pentylsulfonyl)amino, N-ethyl-N-(hexylsulfonyl)amino, N-propyl-N-(methanesulfonyl)amino, N-propyl-N-(ethylsulfonyl)amino, N-propyl-N-(propylsulfonyl)amino, N-propyl-N-(butylsulfonyl)amino, N-propyl-N-(pentylsulfonyl)amino, N-propyl-N-(hexylsulfonyl)amino, N-butyl-N-(methanesulfonyl)amino, N-

butyl-N-(ethylsulfonyl)amino, N-butyl-N-(propylsulfonyl)amino, N-butyl-N-(butylsulfonyl)amino, N-butyl-N-(pentylsulfonyl)amino, N-butyl-N-(hexylsulfonyl)amino, N-pentyl-N-(methanesulfonyl)amino, N-pentyl-N-(ethylsulfonyl)amino, N-pentyl-N-(propylsulfonyl)amino, N-pentyl-N-(butylsulfonyl)amino, N-pentyl-N-(pentylsulfonyl)amino, N-pentyl-N-(hexylsulfonyl)amino, N-hexyl-N-(methanesulfonyl)amino, N-hexyl-N-(ethylsulfonyl)amino, N-hexyl-N-(propylsulfonyl)amino, N-hexyl-N-(butylsulfonyl)amino, N-hexyl-N-(pentylsulfonyl)amino, N-hexyl-N-(hexylsulfonyl)amino, and the like, preferably N-methyl-N-(methanesulfonyl)amino.

Suitable $-CONR^5R^6$ wherein R^5 and R^6 are independently hydrogen or lower alkyl may include carbamoyl, mono(lower)alkylcarbamoyl and di(lower)alkylcarbamoyl. The (lower)alkyl moiety of the mono(lower)alkylcarbamoyl and di(lower)alkylcarbamoyl may be optionally substituted with hydroxy, carboxy, lower alkoxy, (lower)alkoxycarbonyl or halogen atom(s).

Suitable R^5 and R^6 for the above-mentioned $-CONR^5R^6$ may independently include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxymethyl, carboxyethyl, carboxypropyl, carboxybutyl, methoxymethyl, methoxyethyl, methoxypropyl, methoxybutyl, ethoxymethyl, ethoxyethyl, ethoxypropyl, ethoxybutyl, propoxymethyl, propoxyethyl, propoxypropyl, propoxybutyl, butoxymethyl, butoxyethyl, butoxypropyl, butoxybutyl, methoxycarbonylmethyl, methoxycarbonylethyl, methoxycarbonylpropyl, methoxycarbonylbutyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, ethoxycarbonylpropyl, ethoxycarbonylbutyl, propoxycarbonylmethyl, propoxycarbonylethyl,

propoxycarbonylpropyl, propoxycarbonylbutyl, butoxycarbonylmethyl, butoxycarbonylethyl, butoxycarbonylpropyl, butoxycarbonylbutyl, (mono, di or tri)chloromethyl, (mono, di or tri)chloroethyl, (mono, di or tri)fluoromethyl, (mono, di or tri)fluoroethyl, and the like.

Suitable mono(lower)alkylcarbamoyl which may be optionally substituted with hydroxy, carboxy, lower alkoxy, (lower)alkoxycarbonyl or halogen atom(s) may include N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-isopropylcarbamoyl, N-butylcarbamoyl, N-(tert-butyl)carbamoyl, N-(carboxymethyl)carbamoyl, N-(2-carboxyethyl)carbamoyl, N-(carboxypropyl)carbamoyl, N-(ethoxycarbonylmethyl)carbamoyl, N-(ethoxycarbonylethyl)carbamoyl, N-(ethoxycarbonylpropyl)carbamoyl, N-(tert-butoxycarbonylethyl)carbamoyl, N-(methoxyethyl)carbamoyl, N-(hydroxyethyl)carbamoyl or N-(1,1,1-trifluoroethyl)carbamoyl, and the like, preferably N-(2-carboxyethyl)carbamoyl.

Suitable di(lower)alkylcarbamoyl which may be optionally substituted with hydroxy, carboxy, lower alkoxy, (lower)alkoxycarbonyl or halogen atom(s) may include N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-propylcarbamoyl, N-ethyl-N-propylcarbamoyl, N,N-dipropylcarbamoyl, N-(ethoxycarbonylethyl)-N-methylcarbamoyl, N-(methoxycarbonylethyl)-N-methylcarbamoyl, N-(carboxyethyl)-N-methylcarbamoyl, and the like, preferably N,N-dimethylcarbamoyl or N-ethyl-N-methylcarbamoyl.

Suitable $-CONR^5R^6$ wherein R^5 and R^6 together can be four or five methylene groups, of which one methylene group can be replaced by O, N-H or N-(lower)alkyl may include pyrrolidinocarbonyl, piperidinocarbonyl, morpholinocarbonyl, 1-piperadinylcarbonyl, 4-methyl-1-piperadinylcarbonyl, and the like.

Suitable (lower)alkylsulfonylcarbamoyl optionally substituted with cyclo(lower)alkyl or halogen atom(s) in which amine hydrogen is optionally substituted with lower alkyl may include N-(methylsulfonyl)carbamoyl, N-(ethylsulfonyl)carbamoyl, N-(propylsulfonyl)carbamoyl, N-(butylsulfonyl)carbamoyl, N-(pentylsulfonyl)carbamoyl, N-methyl-N-(methylsulfonyl)carbamoyl, N-(ethylsulfonyl)-N-methylcarbamoyl, N-methyl-N-(propylsulfonyl)carbamoyl, N-(butylsulfonyl)-N-methylcarbamoyl, N-methyl-N-(pentylsulfonyl)carbamoyl, N-ethyl-N-(methylsulfonyl)carbamoyl, N-ethyl-N-(ethylsulfonyl)carbamoyl, N-ethyl-N-(propylsulfonyl)carbamoyl, N-(butylsulfonyl)-N-ethylcarbamoyl, N-ethyl-N-(pentylsulfonyl)carbamoyl, N-[(cyclopropylmethyl)sulfonyl]carbamoyl, N-[(cyclopropylethyl)sulfonyl]carbamoyl, N-[(cyclopropylpropyl)sulfonyl]carbamoyl, N-[(cyclobutylmethyl)sulfonyl]carbamoyl, N-[(cyclobutylethyl)sulfonyl]carbamoyl, N-[(cyclobutylpropyl)sulfonyl]carbamoyl, N-[((mono, di or tri)chloromethyl)sulfonyl]carbamoyl, N-[((mono, di or tri)chloroethyl)sulfonyl]carbamoyl, N-[((mono, di or tri)fluoromethyl)sulfonyl]carbamoyl, N-[((mono, di or tri)fluoroethyl)sulfonyl]carbamoyl, and the like, preferably N-(methylsulfonyl)carbamoyl, N-(ethylsulfonyl)carbamoyl, N-(propylsulfonyl)carbamoyl, N-(isopropylsulfonyl)carbamoyl, N-(butylsulfonyl)carbamoyl, N-(pentylsulfonyl)carbamoyl, N-[(cyclopropylmethyl)sulfonyl]carbamoyl and N-[(trifluoromethyl)sulfonyl]carbamoyl, and more preferably N-(ethylsulfonyl)carbamoyl.

Suitable cyclo(lower)alkylsulfonylcarbamoyl may include N-(cyclopropylsulfonyl)carbamoyl, N-

(cyclobutylsulfonyl)carbamoyl, N-(cyclopentylsulfonyl)carbamoyl, N-(cyclohexylsulfonyl)carbamoyl, and the like, preferably N-(cyclopropylsulfonyl)carbamoyl.

Suitable (lower)alkoxycarbonyl may include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, and the like, preferably ethoxycarbonyl.

Suitable lower alkoxy which is substituted with carboxyl or (lower)alkoxycarbonyl may include carboxymethoxy, (methoxycarbonyl)methoxy, (ethoxycarbonyl)methoxy, (propoxycarbonyl)methoxy, (butoxycarbonyl)methoxy, (pentyloxycarbonyl)methoxy, (hexyloxycarbonyl)methoxy, carboxyethoxy, (methoxycarbonyl)ethoxy, (ethoxycarbonyl)ethoxy, (propoxycarbonyl)ethoxy, (butoxycarbonyl)ethoxy, (pentyloxycarbonyl)ethoxy, (hexyloxycarbonyl)ethoxy, carboxypropoxy, (methoxycarbonyl)propoxy, (ethoxycarbonyl)propoxy, (propoxycarbonyl)propoxy, (butoxycarbonyl)propoxy, (pentyloxycarbonyl)propoxy, (hexyloxycarbonyl)propoxy, carboxybutoxy, (methoxycarbonyl)butoxy, (ethoxycarbonyl)butoxy, (propoxycarbonyl)butoxy, (butoxycarbonyl)butoxy, (pentyloxycarbonyl)butoxy, (hexyloxycarbonyl)butoxy, carboxypentyloxy, (methoxycarbonyl)pentyloxy, (ethoxycarbonyl)pentyloxy, (propoxycarbonyl)pentyloxy, (butoxycarbonyl)pentyloxy, (pentyloxycarbonyl)pentyloxy, (hexyloxycarbonyl)pentyloxy, carboxyhexyloxy, (methoxycarbonyl)hexyloxy, (ethoxycarbonyl)hexyloxy, (propoxycarbonyl)hexyloxy, (butoxycarbonyl)hexyloxy, (pentyloxycarbonyl)hexyloxy, (hexyloxycarbonyl)hexyloxy, and

the like, preferably carboxymethoxy and (ethoxycarbonyl)methoxy.

Suitable (lower)alkoxycarbonylamino may include N-methoxycarbonylamino, N-ethoxycarbonylamino, N-propoxycarbonylamino, N-butoxycarbonylamino, N-pentyloxycarbonylamino, N-hexyloxycarbonylamino, and the like, preferably N-ethoxycarbonylamino.

Suitable (lower)alkoxycarbonylamino in which amine hydrogen is substituted with lower alkyl may include N-methyl-N-(methoxycarbonyl)amino, N-methyl-N-(ethoxycarbonyl)amino, N-methyl-N-(propoxycarbonyl)amino, N-methyl-N-(butoxycarbonyl)amino, N-methyl-N-(pentyloxycarbonyl)amino, N-methyl-N-(hexyloxycarbonyl)amino, N-ethyl-N-(methoxycarbonyl)amino, N-ethyl-N-(ethoxycarbonyl)amino, N-ethyl-N-(propoxycarbonyl)amino, N-ethyl-N-(butoxycarbonyl)amino, N-ethyl-N-(pentyloxycarbonyl)amino, N-ethyl-N-(hexyloxycarbonyl)amino, N-propyl-N-(methoxycarbonyl)amino, N-propyl-N-(ethoxycarbonyl)amino, N-propyl-N-(propoxycarbonyl)amino, N-propyl-N-(butoxycarbonyl)amino, N-propyl-N-(pentyloxycarbonyl)amino, N-propyl-N-(hexyloxycarbonyl)amino, N-butyl-N-(methoxycarbonyl)amino, N-butyl-N-(ethoxycarbonyl)amino, N-butyl-N-(propoxycarbonyl)amino, N-butyl-N-(butoxycarbonyl)amino, N-butyl-N-(pentyloxycarbonyl)amino, N-butyl-N-(hexyloxycarbonyl)amino, N-pentyl-N-(methoxycarbonyl)amino, N-pentyl-N-(ethoxycarbonyl)amino, N-pentyl-N-(propoxycarbonyl)amino, N-pentyl-N-(butoxycarbonyl)amino, N-pentyl-N-(pentyloxycarbonyl)amino, N-pentyl-N-(hexyloxycarbonyl)amino, N-hexyl-N-(methoxycarbonyl)amino, N-hexyl-N-(ethoxycarbonyl)amino, N-hexyl-N-(propoxycarbonyl)amino, N-hexyl-N-

(butoxycarbonyl)amino, N-hexyl-N-(pentyloxycarbonyl)amino, N-hexyl-N-(hexyloxycarbonyl)amino, and the like, preferably N-methyl-N-(ethoxycarbonyl)amino.

Suitable aryl(lower)alkyl may include benzyl, phenylethyl, phenylpropyl, phenylbutyl, phenylpentyl, phenylhexyl, naphtylmethyl, naphtylethyl, naphtylpropyl, naphtylbutyl, naphtylpentyl, naphtylhexyl, anthrylmethyl, anthrylethyl, anthrylpropyl, anthrylbutyl, anthrylpentyl, anthrylhexyl, and the like, preferably benzyl.

Suitable aryl(lower)alkoxy may include benzyloxy, phenylethyloxy, phenylpropyloxy, phenylbutyloxy, phenylpentyloxy, phenylhexyloxy, naphtylmethyloxy, naphtylethyloxy, naphtylpropyloxy, naphtylbutyloxy, naphtylpentyloxy, naphtylhexyloxy, anthrylmethyloxy, anthrylethyloxy, anthrylpropyloxy, anthrylbutyloxy, anthrylpentyloxy, anthrylhexyloxy, and the like, preferably benzyloxy.

Suitable arylsulfonylcarbamoyl may include N-(phenylsulfonyl)carbamoyl, N-(naphtylsulfonyl)carbamoyl, N-(anthrylsulfonyl)carbamoyl, and the like, preferably N-phenylsulfonylcarbamoyl.

Suitable ureido in which amine hydrogen is optionally substituted with lower alkyl may include ureido, N-methylureido, N'-methylureido, N,N'-dimethylureido, N',N'-dimethylureido, N,N',N'-trimethylureido, N-ethylureido, N'-ethylureido, N,N'-diethylureido, N',N'-diethylureido, N,N',N'-triethylureido, N-propylureido, N'-propylureido, N,N'-dipropylureido, N',N'-dipropylureido, N,N',N'-tripropylureido, N-butylureido, N'-butylureido, N,N'-dibutylureido, N',N'-

dibutylureido, N,N',N'-tributylureido, N-pentylureido, N'-pentylureido, N,N'-dipentylureido, N',N'-dipentylureido, N,N',N'-tripentylureido, N-hexylureido, N'-hexylureido, N,N'-dihexylureido, N',N'-dihexylureido, N,N',N'-trihexylureido, N-methyl-N'-ethylureido, N-methyl-N',N'-diethylureido, N-methyl-N,N'-diethylureido, N-ethyl-N',N'-dimethylureido, N-ethyl-N'-methylureido, N-ethyl-N',N'-dimethylureido, N-ethyl-N,N'-dimethylureido, and the like, preferably ureido, N-methylureido, N'-methylureido, N',N'-dimethylureido, N,N'-dimethylureido or N,N',N'-trimethylureido.

Amino protective groups in the context of the invention are the customary amino protective groups used in peptide chemistry. These include benzyl, benzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, allyloxycarbonyl, phthaloyl, 2,2,2-trichloroethoxycarbonyl, fluorenyl-9-methoxycarbonyl, formyl, acetyl, 2-chloroacetyl, 2,2,2-trifluoroacetyl, 2,2,2-trichloroacetyl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, phthalimido, isovaleroyl or benzyloxymethylene, 4-nitrobenzyl, 2,4-dinitrobenzyl, 4-nitrophenyl, 4-methoxyphenyl, triphenylmethyl, and the like, preferably benzyl.

Suitable salts of the object aminoalcohol derivatives [I] are pharmaceutically acceptable salts and include conventional non-toxic salts such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, oxalate, maleate, fumarate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an alkali metal salt [e.g. sodium salt, potassium salt, etc.], and the like, preferably hydrochloride.

Preferred embodiment of the object compound [I] is as follows:

X_1 is $-OCH_2-$;

X_2 is $-CH_2-$;

X_3 is $-O-$;

R^1 is phenyl optionally substituted with one or two substituent(s) selected from the group consisting of hydroxy, halogen, nitro, amino, formyl, (lower)alkylsulfonylamino, aryl(lower)alkoxy and hydroxy(lower)alkyl;

R^2 is hydrogen; and

R^3 is hydroxy(lower)alkyl.

More preferred embodiment of the object compound [I] is as follows:

R^4 is 4-quinolyl optionally substituted with one or two substituent(s) selected from the group consisting of fluoro, carboxy, nitro, amino, halo(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxycarbonyl,
(lower)alkylsulfonylcarbamoyl optionally substituted with cyclo(lower)alkyl or halogen atom(s) in which amine hydrogen is optionally substituted with lower alkyl,
cyclo(lower)alkylsulfonylcarbamoyl,
arylsulfonylcarbamoyl,
(lower)alkylcarbonylamino in which amine hydrogen is optionally substituted with lower alkyl,
lower alkoxy optionally substituted with carboxy or (lower)alkoxycarbonyl,
(lower)alkylsulfonylamino in which amine hydrogen is optionally substituted with lower alkyl,
ureido in which amine hydrogen(s) is(are) optionally substituted with lower alkyl,
(lower)alkoxycarbonylamino in which amine hydrogen is

optionally substituted with lower alkyl, and

$-CONR^5R^6$

(wherein R^5 and R^6 are independently hydrogen or lower alkyl optionally substituted with hydroxy, carboxy, lower alkoxy, (lower)alkoxycarbonyl or halogen atom(s), or R^5 and R^6 together can be four or five methylene groups, of which one methylene group can be replaced by O, N-H or N-(lower)alkyl).

More preferred embodiments of the object compound [I] are as follows:

(1) N-[[4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-1-propanesulfonamide,

(2) N-[[4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-beta-alanine, and

(3) N-(2-Hydroxyethyl)-4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-8-quinolinecarboxamide,

or a pharmaceutically acceptable salt thereof.

The processes for preparing the object compound [I] are explained in detail in the following.

Process 1

The object compound [I] or a salt thereof can be prepared by reacting a compound [II] with a compound [III] or a salt thereof.

Suitable salt of the compound [III] is the same as those exemplified for the compound [I].

The reaction is preferably carried out in the presence

of a base such as an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkaline earth metal carbonate [e.g. magnesium carbonate, calcium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], tri(lower)alkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, and the like.

The reaction is usually carried out in a conventional solvent such as an alcohol [e.g. methanol, ethanol, propanol, isopropanol, etc.], diethyl ether, tetrahydrofuran, dioxane, or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction can be carried out under cooling to heating.

The reaction can be carried out in the manner disclosed in Examples 16, 18, 41, etc. or in a similar manner to these examples.

Process 2

The object compound [Ib] or a salt thereof can be prepared by subjecting a compound [Ia] or a salt thereof to elimination reaction of the amino protective group.

Suitable salts of the compounds [Ia] and [Ib] may be the same as those exemplified for the compound [I].

This reaction can be carried out in the manner disclosed in Examples 17, 21, 37, etc. or in a similar manner to these examples.

Process 3

The object compound [Ic] or a salt thereof can be prepared by reacting a compound [IV] or a salt thereof with a compound [V].

Suitable salts of the compound [IV] may be the same as those exemplified for the compound [I].

The reaction can be also carried out in the manner disclosed in Examples 23, 25, 35, etc. or in a similar manner to these examples.

The compounds obtained by the above processes are optionally converted to other compounds within the scope of the invention, in the manners disclosed in Examples 42, 50, etc.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, and the like, and converted to a desired salt in conventional manners, if necessary.

It is to be noted that the compound [I] and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixtures thereof are included within the scope of the present invention.

It is further to be noted that isomerization or rearrangement of the object compound [I] may occur due to the effect of the light acid, base, and the like, and the compound obtained as the result of said isomerization or rearrangement is also included within the scope of the present invention.

It is also to be noted that the solvating form of the compound [I] (e.g. hydrate, etc.) and any form of crystals of the compound [I] are included within the scope of the present invention.

The object compound [I] or a salt thereof possesses gut sympathomimetic, anti-ulcerous, anti-pancreatitis, lipolytic, anti-urinary incontinence and anti-pollakiuria activities, and are useful for the treatment and/or prevention of gastro-intestinal disorders caused by smooth muscle contractions in human beings or animals, and more particularly for the

treatment and/or prevention of spasm or hyperanakinesia in case of irritable bowel syndrome, gastritis, gastric ulcer, duodenal ulcer, enteritis, cholecystopathy, cholangitis, urinary calculus, and the like; for the treatment and/or prevention of ulcer such as gastric ulcer, duodenal ulcer, peptic ulcer, ulcer causes by non steroidal anti-inflammatory drugs, and the like; for the treatment and/or prevention of dysuria such as pollakiuria, urinary incontinence, and the like in case of nervous pollakiuria, neurogenic bladder dysfunction, nocturia, unstable bladder, cystospasm, chronic cystitis, chronic prostatitis, prostatic hypertrophy, and the like; and for the treatment and/or prevention of pancreatitis, obesity, diabetes, glycosuria, hyperlipidemia, hypertension, atherosclerosis, glaucoma, melancholia, depression, and the like; for the treatment and/or prevention of diseases as the result of insulin resistance (e.g. hypertension, hyperinsulinemia, etc.); for the treatment and/or prevention of neurogenetic inflammation; and for reducing a wasting condition, and the like.

Additionally, β_3 adrenergic receptor agonists are known to lower triglyceride and cholesterol levels and to raise high density lipoprotein levels in mammals (US Patent No. 5,451,677). Accordingly, the object compound [I] is useful in the treatment and/or prevention of conditions such as hyper-triglyceridaemia and hypercholesterolaemia, and in lowering high density lipoprotein levels as well as in the treatment of atherosclerotic and cardiovascular diseases and related conditions.

Moreover, the object compound [I] is useful for inhibiting uterine contractions, preventing premature labor, and treating and preventing dysmenorrhea.

The object compound (I) or a pharmaceutically acceptable

salt thereof can be usually administered to mammals including human being in the form of a conventional pharmaceutical composition such as capsule, micro-capsule, tablet, granule, powder, troche, syrup, aerosol, inhalation, solution, injection, suspension, emulsion, suppository, and the like.

The effective ingredient may be usually administered in a unit dose of 0.01 mg/kg to 50 mg/kg, one to four times a day.

However, the above dosage may be increased or decreased according to age, weight and conditions of patients or methods of administration.

In order to show the usefulness of the ethanolamine derivative in the present invention for the prophylactic and therapeutic treatment of the above-mentioned diseases in a human being or an animal, the pharmacological test data of the representative compound thereof is shown in the following.

Test

Effect on the increase in intravesical pressure induced by carbachol in anesthetized dog

Test Compound

(1) (2S)-2-[N-[(2S)-2-Hydroxy-3-phenoxypropyl]amino]-3-[4-(1-phthalazinyloxy)phenyl]propan-1-ol

(This compound is the object compound of Example 25.)

Test Method

Female Beagle dogs weighing 8.0-15.0 kg were fasted for 24 hours and maintained under halothane anesthesia. A 12F Foley catheter was lubricated with water-soluble jelly, inserted into the urethral orifice and advanced approximately 10 cm until the balloon tip was placed well inside the bladder.

The balloon was then inflated with 5 ml of room air and catheter was slowly withdrawn just part the first resistance that is felt at the bladder neck. Urine was completely drained out thorough the catheter, and 30 ml of biological saline was infused. The catheter was connected to pressure transducer, and intravesical pressure was continuously recorded. Intraduodenal administration of test compound (1) inhibited carbachol-induced (1.8 μg/kg) increase in intravesical pressure (IVP).

Test Results

Treatment	% Inhibition of carbachol-induced increase in IVP
Test Compound (1) (0.32 mg/kg)	35.9%

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

Under nitrogen, to a solution of 4-((2S)-2-amino-3-hydroxypropyl)phenol hydrochloride (5.0 g) in methanol (50 ml) was added 28% sodium methoxide in methanol (4.7 ml) at 5°C, and the mixture was stirred at the same temperature for 10 minutes. After removal of insoluble materials by filtration, the filtrate was evaporated and dried in vacuo. A mixture of the residue and benzaldehyde (2.5 ml) in toluene (50 ml) in the presence of a catalytic amount of p-toluenesulfonic acid monohydrate was refluxed for 2 hours to remove water as the toluene azeotrope, and then the mixture was evaporated in vacuo. To a solution of the residue in methanol (50 ml) was

added sodium borohydride (930 mg) under nitrogen at 5°C, and the mixture was stirred at the same temperature for 1 hour. The reaction mixture was poured into ice-cold water with stirring. After 20 minutes, ethyl acetate and brine were added, followed by separation. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1 to 10 : 1) to give 4-((2S)-2-benzylamino-3-hydroxypropyl)-phenol (6.3 g).

^{1}H NMR (200MHz, DMSO-d_6) : δ 2.45-2.75 (3H, m), 3.15-3.45 (2H, m), 3.73 (2H, s), 6.6-6.7 (2H, m), 6.9-7.0 (2H, m), 7.15-7.35 (5H, m)

Preparation 2

To a solution of 4-((2S)-2-benzylamino-3-hydroxypropyl)-phenol (4.00 g) in ethanol (80 ml) was added (2S)-3-phenoxy-1,2-epoxypropane (2.56 g) and the solution was refluxed for 7 hours. After cooling to room temperature, the solvent was removed by evaporation and the residue was chromatographed on a 350 g of silica gel (eluent : chloroform/methanol = 9/1) to give 4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]-3-hydroxypropyl]phenol (4.89g) as a white foam.

MS m/z : 408 (MH^+)

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.67 (br, 2H), 2.46 (dd, J=8.9, 13.7Hz, 1H), 2.75-2.97 (m, 4H), 3.04-3.16 (m, 1H), 3.45-3.57 (m, 2H), 3.66 (d, J=13.5Hz, 1H), 3.74-3.90 (m, 3H), 3.92 (d, J=13.5Hz, 1H), 6.68 (d, J=8.4Hz, 2H), 6.81 (d, J=7.8Hz, 2H), 6.92-6.98 (m, 1H), 6.94 (d, J=8.4Hz, 2H), 7.20-7.34 (m, 7H)

Preparation 3

The following compounds were obtained in a manner similar to Preparation 2.

(1) 4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenol

^{1}H NMR (200MHz, $CDCl_3$) : δ 2.4-2.95 (4H, m), 3.0-3.2 (1H, m), 3.45-3.9 (4H, m), 4.3-4.45 (1H, m), 6.66 (2H, d, J=8.4Hz), 6.85 (2H, d, J=8.4Hz), 6.95-7.4 (9H, m)

(2) 4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(4-benzyloxy-3-nitrophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenol

^{1}H NMR (200MHz, $CDCl_3$) : δ 2.5-2.95 (4H, m), 3.1-3.25 (1H, m), 3.5-3.9 (4H, m), 4.3-4.4 (1H, m), 5.16 (2H, s), 6.71 (2H, d, J=8.4Hz), 6.9-7.0 (3H, m), 7.1-7.5 (11H, m), 7.62 (1H, d, J=2.1Hz)

Preparation 4

Under nitrogen, to a suspension of 4-chloroquinoline-7-carboxylic acid (150 mg) in N,N-dimethylformamide (7.5 ml) was added carbonyldiimidazole (141 mg) at room temperature and the mixture was stirred at the same temperature for 30 minutes. To this one was added methylamine (60% in methanol, 62μl) and the mixture was stirred at room temperature for 3.5 hours. The mixture was poured into a mixture of water and ethyl acetate. After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure to make a solid. The residue was washed with hexane by decantation, followed by drying in vacuo to give 4-chloroquinoline-7-carboxylic acid methylamide (135 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 2.87 (3H, d, J=4.5Hz), 7.86 (1H, d, J=4.7Hz), 8.1-8.2 (1H, m), 8.29 (1H, d, J=8.8Hz), 8.62 (1H, s), 8.94 (1H, d, J=4.7Hz)

Preparation 5

Under nitrogen, to a suspension of 4-chloroquinoline-7-carboxylic acid (200 mg) in N,N-dimethylformamide (20 ml) was added carbonyldiimidazole (187 mg) at room temperature and the mixture was stirred at the same temperature for 30 minutes. To this one were added dimethylamine hydrochloride (94 mg) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.17 ml), and the mixture was stirred at room temperature for 3 hours. The mixture was poured into a mixture of water and dichloromethane. After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was dried in vacuo to give 4-chloroquinoline-7-carboxylic acid dimethylamide (247 mg).
^{1}H NMR (200MHz, $CDCl_3$) : δ 3.05 (3H, s), 3.19 (3H, s), 7.5-7.55 (1H, m), 7.72 (1H, ABq, J=1.6, 8.6Hz), 8.15 (1H, d, J=1.3Hz), 8.30 (1H, d, J=8.6Hz), 8.84 (1H, d, J=4.7Hz)

Preparation 6

Under nitrogen, to a suspension of 4-chloroquinoline-7-carboxylic acid (300 mg) in N,N-dimethylformamide (15 ml) was added carbonyldiimidazole (282 mg) at room temperature and the mixture was stirred at the same temperature for 30 minutes. To this one were added methanesulfonamide (165 mg) and 1,8-diazabicyclo[5.4.0]-7-undecene (0.26 ml) and the mixture was stirred at room temperature for 3.5 hours. The mixture was poured into a mixture of aqueous 0.1N hydrochloric acid and ethyl acetate. After separation, the aqueous layer was extracted with ethyl acetate five times. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was triturated with a mixture of methanol, chloroform and diisopropyl ether. The precipitates were collected and dried in vacuo to give N-(4-chloroquinoline-7-carbonyl)-methanesulfonamide (230 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 3.45 (3H, s), 7.92 (1H, d, J=4.7Hz), 8.20 (1H, ABq, J=1.7, 8.8Hz), 8.34 (1H, d, J=8.8Hz), 8.74 (1H, d, J=1.5Hz), 8.99 (1H, d, J=4.7Hz)

Preparation 7

To a solution of 4-chloroquinoline-7-carboxylic acid (2.6 g) was added potassium hydroxide (870 mg) at room temperature, and the mixture was stirred at the same temperature for 12 hours. The mixture was evaporated and dried in vacuo. Under nitrogen, to a solution of the potassium salts in N,N-dimethylformamide (60 ml) was added iodoethane (1.0 ml) at room temperature, and the mixture was stirred at 80°C for 1.5 hours. The mixture was poured into ice-cold water with stirring to generate a precipitate. After stirred for 20 minutes, the precipitate was collected by filtration and immediately the filter cake was dissolved in ethyl acetate. The solution was dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel (toluene : ethyl acetate = 20 : 1 to 5 : 1) to give ethyl 4-chloroquinoline-7-carboxylate (2.3 g).

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.46 (3H, t, J=7.1 Hz), 4.48 (2H, q, J=7.1 Hz), 7.59 (1H, d, J=4.7Hz), 8.2-8.35 (2H, m), 8.85-8.9 (2H, m)

Preparation 8

A mixture of ethyl 4-chloroquinoline-7-carboxylate (470 mg) and 2M ammonium hydroxide in methanol (30 ml) was sealed with stirring at 100°C for 60 hours. The reaction mixture was evaporated and dried in vacuo to give 4-chloroquinoline-7-carboxylic acid amide (420 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 7.86 (1H, d, J=4.7Hz), 8.15-8.45 (2H, m), 8.65 (1H, d, J=1.3Hz), 8.94 (1H, d, J=4.7Hz)

Preparation 9

Under nitrogen, to 4-chloro-8-trifluoromethylquinoline (5 g) was added slowly fuming sulfonic acid (33%, 22 ml) at 50°C, and the mixture was stirred at 100°C for 6 hours. The mixture was added to ice water carefully. The aqueous mixture was adjusted to pH 10 with ammonia water. After removal of insoluble materials by filtration, the filtrate was controlled to pH 3 - 4 with concentrated hydrochloric acid. The precipitates were collected and dried in vacuo to give 4-chloroquinoline-8-carboxylic acid (950 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 7.95-8.05 (1H, m), 8.07 (1H, d, J=5.0Hz), 8.5-8.65 (2H, m), 9.06 (1H, d, J=4.9Hz)

Preparation 10

Under nitrogen, a mixture of 4-chloroquinoline-8-carboxylic acid (447 mg) and thionyl chloride (3 ml) in the presence of one drop of N,N-dimethylformamide was refluxed for 30 minutes. The mixture was evaporated under reduced pressure to remove the volatile materials, and dried in vacuo to give the crude acid chloride.

Under nitrogen, to a suspension of the above obtained acid chloride in dichloromethane (10 ml) was added ammonia (6.8M in ethanol, 2 ml) at 5°C, and the mixture was stirred at room temperature for 1 hour. To this one was added methanol (20 ml) and the mixture was stirred at room temperature for 6 hours. After evaporation under reduced pressure, the residue was dissolved in a mixture of dichloromethane and water, followed by separation. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform : ethyl acetate = 20 : 1 to 10 : 1) to give 4-chloroquinoline-8-carboxylic acid amide (140 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 7.85-7.9 (1H, m), 7.92 (1H, d, J=4.6Hz), 8.44 (1H, ABq, J=1.5, 8.4Hz), 8.60 (1H, ABq, J=1.5, 7.3Hz), 8.98 (1H, d, J=4.8Hz)

Preparation 11

Under nitrogen, to a solution of [(1S)-1-hydroxymethyl-2-(4-hydroxyphenyl)ethyl]carbamic acid tert-butyl ester (24 g) in dichloromethane (500 ml) were added 2,2-dimethoxypropane (34 ml) and p-toluenesulfonic acid monohydrate (1.7 g) at room temperature, and the mixture was stirred at the same temperature for 60 hours. The resulting mixture was poured into saturated aqueous sodium hydrogencarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo to get a solid. To the solid was added hexane so as to triturate and then the slurry was stirred for 12 hours, followed by filtration and drying in vacuo to give (4S)-4-(4-hydroxybenzyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (22 g).

^{1}H NMR (200MHz, DMSO-d_6) : δ 1.3-1.55 (15H, m), 2.4-2.6 (1H, m), 2.8-2.95 (1H, m), 3.6-4.0 (3H, m), 6.69 (2H, d, J=8.2Hz), 6.98 (2H, d, J=8.4Hz)

Preparation 12

Under nitrogen, to a solution of (4S)-4-(4-hydroxybenzyl)-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (10 g) in dichloromethane (100 ml) were added 2,6-lutidine (4.2 ml) and trifluoromethanesulfonic anhydride (6.0 ml) at 5°C, and the mixture was stirred at the same temperature for 80 minutes. The reaction mixture was poured into ice-cold 0.1N hydrochloric acid and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium

hydrogencarbonate, water and brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 10 : 1) to give tert-butyl (4S)-2,2-dimethyl-4-(4-trifluoromethanesulfonyloxybenzyl)oxazolidine-3-carboxylate (13 g).

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.35-1.7 (15H, m), 2.65-2.85 (1H, m), 3.05-3.3 (1H, m), 3.7-4.2 (3H, m), 7.15-7.4 (4H, m)

Preparation 13

Under nitrogen, to a solution of tert-butyl (4S)-2,2-dimethyl-4-(4-trifluoromethanesulfonyloxybenzyl)oxazolidine-3-carboxylate (2.2 g) in toluene (55 ml) were added aniline (0.55 ml), cesium carbonate (2.3 g), tris(dibenzylideneacetone)-dipalladium(0) (46 mg) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (94 mg) at room temperature and the mixture was stirred at 80°C for 31 hours. The mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 10 : 1 to 8 : 1) to give tert-butyl (4S)-2,2-dimethyl-4-[4-(phenylamino)benzyl]-oxazolidine-3-carboxylate (955 mg).

(+)ESI-MS m/s : 405 $(M+Na)^+$

Preparation 14

To a solution of tert-butyl (4S)-2,2-dimethyl-4-[4-(phenylamino)-benzyl]oxazolidine-3-carboxylate (949 mg) in a mixture of 1,4-dioxane (5 ml) and methanol (5 ml) was added 4N hydrogen chloride in 1,4-dioxane (10 ml) at room temperature, and the mixture was stirred at room temperature for 9 hours. After evaporation under reduced pressure, the residue was

dried in vacuo to give (2S)-2-amino-3-[4-(phenylamino)phenyl]propan-1-ol hydrochloride (788 mg).
(+)APCI-MS m/s : 243 $(M-HCl+H)^+$

Preparation 15

Under nitrogen, to a solution of (2S)-2-amino-3-[4-(phenylamino)phenyl]propan-1-ol hydrochloride (773 mg) in methanol (10 ml) was added sodium methoxide (28% in methanol, 0.53 ml) at room temperature, and the mixture was stirred at the same temperature for 15 minutes. After removal of insoluble materials by filtration, the filtrate was evaporated and dried in vacuo. A mixture of the residue and benzaldehyde (0.28 ml) in a mixture of toluene (10 ml) and N,N-dimethylformamide (5 ml) in the presence of a catalytic amount of p-toluenesulfonic acid monohydrate was refluxed for 3 hours to remove water as the toluene azeotrope. After the mixture was cooled to 5°C, to this one was added sodium borohydride (105 mg) under nitrogen at 5°C, followed by addition of methanol (10 ml) dropwise. The mixture was stirred at room temperature overnight. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography on silica gel (chloroform : methanol = 50 : 1 to 20 : 1) to give (2S)-2-benzylamino-3-[4-(phenylamino)-phenyl]propan-1-ol (367 mg).
(+)APCI-MS m/s : 333 $(M+H)^+$

Preparation 16

Under nitrogen, to a solution of 4-(hydroxymethyl)phenol (20 g) in N,N-dimethylformamide (400 ml) were added triethylamine (56 ml) and methanesulfonyl chloride (27.4 ml)

at 5°C, and the mixture was stirred at the same temperature for 4 days. The mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1 to 2 : 1) to give methanesulfonic acid 4-(chloromethyl)phenyl ester (11.37 g).

(+)ESI-MS m/s : 243, 245 $(M+Na)^+$

Preparation 17

Under nitrogen, a solution of methanesulfonic acid 4-(chloromethyl)phenyl ester (14.2 g) and triphenylphosphine (16.9 g) in toluene (150 ml) was refluxed for 24 hours. The precipitates were collected by filtration, washed with toluene and dried in vacuo to give [4-(methanesulfonyloxy)benzyl]-triphenylphosphonium chloride (21.06 g).

(+)APCI-MS m/s : 447, 449 $(M-Cl)^+$

Preparation 18

Under nitrogen, to a suspension of [4-(methanesulfonyloxy)-benzyl]triphenylphosphonium chloride (19.7 g) in N,N-dimethylformamide (85 ml) was added small portions of potassium t-butoxide (4.99 g) at 5°C, and the mixture was stirred at the same temperature for 30 minutes. To this one was added a solution of tert-butyl (4R)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate (8.49 g) in tetrahydrofuran (50 ml) dropwise. After stirring at the same temperature for 4 hours, the mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The

residue was purified by column chromatography on silica gel (chloroform : ethyl acetate = 100 : 1 to 20 : 1) to give tert-butyl cis-(4S)-4-[2-[4-(methanesulfonyloxy)phenyl]vinyl]-2,2-dimethyloxazolidine-3-carboxylate (2.25 g), tert-butyl trans-(4S)-4-[2-[4-(methanesulfonyloxy)phenyl]vinyl]-2,2-dimethyloxazolidine-3-carboxylate (1.76 g) and the mixture of cis-form and trans-form (8.18 g).

cis-form ^{1}H NMR (200MHz, $CDCl_3$) : δ 1.2-1.7 (15H, m), 3.14 (3H, s), 3.7-3.9 (1H, m), 4.0-4.2 (1H, m), 4.7-4.9 (1H, m), 5.75 (1H, ABq, J=9.4, 11.7Hz), 6.50 (1H, d, J=11.7Hz), 7.1-7.4 (4H, m)

trans-form ^{1}H NMR (200MHz, $CDCl_3$) : δ 1.3-1.7 (15H, m), 3.14 (3H, s), 3.83 (1H, ABq, J=2.2, 9.0Hz), 4.05-4.2 (1H, m), 4.35-4.7 (1H, m), 6.15 (1H, ABq, J=7.6, 15.6Hz), 6.4-6.7 (1H, m), 7.23 (2H, d, J=8.6Hz), 7.41 (2H, d, J=8.7Hz)

Preparation 19

A mixture of tert-butyl cis- and trans-(4S)-4-[2-[4-(methanesulfonyloxy)phenyl]vinyl]-2,2-dimethyloxazolidine-3-carboxylate (8.18 g) and 10% palladium on activated carbon (50% wet, 1 g) in methanol (80 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 3.5 hours. After filtration, the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 4 : 1 to 1 : 1) to give methanesulfonic acid 4-[(3S)-3-(tert-butoxycarbonylamino)-4-hydroxybutyl]phenyl ester (5.66 g).

(+) ESI-MS m/s : 382 $(M+Na)^+$

Preparation 20

Under nitrogen, to a solution of methanesulfonic acid 4-[(3S)-3-(tert-butoxycarbonylamino)-4-hydroxybutyl]phenyl ester (5.66 g) in dichloromethane (60 ml) were added 2,2-

dimethoxypropane (3.87 ml) and p-toluenesulfonic acid monohydrate (300 mg) at room temperature, and the mixture was stirred at the same temperature overnight. The resulting mixture was poured into saturated aqueous sodium hydrogencarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 5 : 1 to 2 : 1) to give tert-butyl (4S)-4-[2-[4-(methanesulfonyloxy)-phenyl]ethyl]-2,2-dimethyloxazolidine-3-carboxylate (5.26 g).
(+) APCI-MS m/s : 300 $(M-Boc+2H)^+$

Preparation 21

A mixture of (4S)-4-[2-[4-(methanesulfonyloxy)phenyl]-ethyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (5.26 g) and aqueous 1N sodium hydroxide (65.8 ml) in a mixture of 1,4-dioxane (150 ml) and water (50 ml) was refluxed for 1 hour. The mixture was diluted with ethyl acetate. After separation, the organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure to turn out to be a solid. The solid was washed with hexane and dried in vacuo to give (4S)-4-[2-(4-hydroxyphenyl)ethyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (3.37 g).
(+)ESI-MS m/s : 344 $(M+Na)^+$

Preparation 22

Under nitrogen, to a solution of (4S)-4-[2-(4-hydroxyphenyl)ethyl]-2,2-dimethyloxazolidine-3-carboxylic acid tert-butyl ester (200 mg) in dimethyl sulfoxide (5 ml) was added potassium tert-butoxide (76.8 mg) at room temperature. After stirring at the same temperature for 10 minutes, to this

one was added 4-chloroquinoline (112 mg), and the mixture was stirred at 104°C for 1 hour. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate =4 : 1 to 1 : 1) to give (4S)-2,2-dimethyl-4-[2-[4-(quinolin-4-yloxy)phenyl]ethyl]oxazolidine-3-carboxylic acid tert-butyl ester (278 mg).

(+) ESI-MS m/s : 449 $(M+H)^+$

Preparation 23

To a solution of (4S)-2,2-dimethyl-4-[2-[4-(quinolin-4-yloxy)phenyl]ethyl]oxazolidine-3-carboxylic acid tert-butyl ester (275 mg) in a mixture of 1,4-dioxane (1 ml) and methanol (1 ml) was added 4N hydrogen chloride in 1,4-dioxane (2 ml) at room temperature, and the mixture was stirred at room temperature overnight. After evaporation under reduced pressure, the residue was dried in vacuo to give (2S)-2-amino-4-[4-(quinolin-4-yloxy)phenyl]butan-1-ol dihydrochloride (239.9 mg).

(+) ESI-MS m/s: 309 $(M-2HCl+H)^+$

Preparation 24

To a solution of 4-[(2S)-2-[N-benzyl-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenol (300 mg) in a mixed solvent of methanol (7.0 ml) and chlorobenzene (7.0 ml) was added 10% palladium on activated carbon (50% wet, 150 mg) and the mixture was hydrogenated at 1 atm for 2 hours. The mixture was filtered, washed with methanol, and concentrated in vacuo to give 4-[(2S)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]-phenol hydrochloride (264 mg) as a yellow solid.

^{1}H NMR (200MHz, DMSO-d_6) : δ 2.67-3.63 (m, 7H), 5.05 (br, 1H), 5.38 (br, 1H), 6.35 (d, J=4.2Hz, 1H), 6.72 (d, J=8.3Hz, 1H), 7.07 (d, J=8.3Hz, 1H), 7.24-7.48 (m, 4H), 8.47 (br, 1H), 9.24 (br, 1H), 9.37 (br, 1H)

Preparation 25

To a solution of L-tyrosinol hydrochloride (2.29 g) in ethanol (45 ml) were successively added N,N-diisopropylethylamine (2.34 ml) and (2S)-3-phenoxy-1,2-epoxypropane (1.69 g). The mixture was refluxed for 5 hours. After cooling to room temperature, the solvent was removed by evaporation. The residual paste was dissolved in ethyl acetate (50 ml) and the solution was washed successively with water (50 ml×2) and brine (50 ml×1). The combined washes were further extracted with ethyl acetate (20 ml×1) and the extract was washed with brine (20 ml×1). The organic layers were combined, dried over magnesium sulfate, filtered, and evaporated to give a white solid (2.91 g). The crude solid was recrystallized from a refluxing mixture of chloroform (15 ml) and ethyl acetate (5 ml) to give 4-[(2S)-3-hydroxy-2-[[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenol (1.49 g) as a white powder.

MS m/z : 318 (MH^+)

Preparation 26

To a solution of (4S)-2,2-dimethyl-4-[4-(trifluoromethanesulfonyloxy)benzyl]oxazolidine-3-carboxylic acid tert-butyl ester (3.0 g) in methanol (15 ml) was added 4N hydrogen chloride in dioxane (10 ml) at room temperature, and the solution was stirred at the same temperature for 3 hours. The mixture was evaporated in vacuo, and the residue was triturated with diisopropyl ether to give trifluoromethanesulfonic acid 4-[(2S)-2-amino-3-

hydroxypropyl]phenyl ester hydrochloride (2.48 g) as a colorless powder.

MS m/z : 300 (M+1)

^{1}H NMR (200MHz, DMSO-d_6) : δ 2.80-3.10 (2H, m), 3.30-3.60 (3H, m), 5.30-5.40 (1H, br-s), 7.47 (4H, s)

Preparation 27

A solution of trifluoromethanesulfonic acid 4-[(2S)-2-amino-3-hydroxypropyl]phenyl ester hydrochloride (2.48 g) in methanol (15 ml) was added 28% sodium methylate (1.42 ml) and stirred at room temperature for 1 hour. The mixture was evaporated in vacuo. To the residue were added benzaldehyde (784 mg), toluene (30 ml) and a catalytic amount of p-toluenesulfonic acid monohydrate and refluxed for 2 hours to remove water as the toluene azeotrope, and then the mixture was evaporated in vacuo. To the residue in methanol (60 ml) was added sodium borohydride (335 mg) under nitrogen at 5°C, and the mixture was stirred at room temperature for 2 hours. The resulting mixture was poured into ice-cold water and stirred for 30 minutes before adding ethyl acetate and brine. After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (hexane-ethyl acetate-methanol) over silica gel to afford trifluoromethanesulfonic acid 4-[(2S)-2-benzylamino-3-hydroxypropyl]phenyl ester (1.85 g) as a colorless powder.

MS m/z : 390 (M+1)

^{1}H-NMR (200MHz, $CDCl_3$) : δ 2.70-3.05 (3H, m), 3.34 (1H, dd, J=4.7, 10.7Hz), 3.65 (1H, dd, J=3.7, 10.7Hz), 3.80-3.90 (2H, m), 6.70-7.40 (9H, m)

Preparation 28

Under nitrogen, a solution of trifluoromethanesulfonic

acid 4-[(2S)-2-benzylamino-3-hydroxypropyl]phenyl ester (1.85 g), (2S)-3-phenoxy-1,2-epoxypropane (713 mg) in ethanol (10 ml) was refluxed for 24 hours. The mixture was evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 3 : 1 to 1 : 1) to give trifluoromethanesulfonic acid 4-[(2S)-3-hydroxy-2-[N-benzyl-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenyl ester (2.0 g) as a colorless foam.

MS m/z : 540 (M+1)

^{1}H NMR (200MHz, $CDCl_3$) : δ 2.50-3.15 (6H, m), 3.50-4.00 (7H, m), 6.80-7.05 (3H, m), 7.20-7.30 (14H, m)

Preparation 29

To a solution of N-benzyl-N-[2-(4-nitrophenyl)ethyl]-amine (1.70 g) in ethanol (34 ml) was added (2S)-2-(phenoxymethyl)oxirane (1.10 g) and the solution was refluxed for 5 hours. After cooling to room temperature, the solvent was removed by evaporation. The residue (2.87 g) was chromatographed on 90 g of silica gel (hexane : ethyl acetate = 9 : 1) to give (2S)-1-[N-benzyl-N-[2-(4-nitrophenyl)ethyl]-amino]-3-phenoxypropan-2-ol (2.62 g) as a yellow oil.

MS m/z : 407 (MH^+)

^{1}H NMR (200MHz, $CDCl_3$) : δ 2.72-2.94 (m, 6H), 3.06 (br, 1H), 3.60 (d, J=13.5Hz, 1H), 3.83 (d, J=13.5Hz, 1H), 3.89-3.92 (m, 2H), 4.00-4.06 (m, 1H), 6.84-6.96 (m, 3H), 7.18-7.32 (m, 9H), 8.05-8.10 (m, 2H)

Preparation 30

To a solution of (2S)-1-[N-benzyl-N-[2-(4-nitrophenyl)-ethyl]amino]-3-phenoxypropan-2-ol (2.55 g) in a mixed solvent of ethanol (60 ml) and water (20 ml) were added iron powder (1.05 g) and ammonium chloride (168 mg). The solution was refluxed for 1.5 hours. After cooling to room temperature,

the metal was filtered off with a Celite cake and washed with ethanol. The filtrate was concentrated in vacuo and the residue was partitioned between ethyl acetate (50 ml) and a saturated solution of sodium hydrogencarbonate in water (50 ml). The separated organic layer was washed with brine (50 ml) and dried over magnesium sulfate. Filtration followed by evaporation gave (2S)-1-[N-[2-(4-aminophenyl)ethyl]-N-benzylamino]-3-phenoxypropan-2-ol (2.43 g) as a yellow oil.
MS m/z : 377 (MH^+)
^1H NMR (200MHz, $CDCl_3$) : δ 2.60-2.86 (m, 6H), 3.31 (br, 1H), 3.55 (br, 2H), 3.59 (d, J=13.6Hz, 1H), 3.82-4.04 (m, 4H), 6.59 (d, J=6.4Hz, 2H), 6.85-6.97 (m, 5H), 7.23-7.34 (m, 7H)

Preparation 31

The following compounds were obtained in a manner similar to Preparation 4.

(1) 4-Chloro-N-ethyl-N-methyl-7-quinolinecarboxamide
MS m/z : 271 ($M+Na^+$)

(2) 4-Chloro-N-propyl-7-quinolinecarboxamide
MS m/z : 249 (MH^+), 271 ($M+Na^+$)

(3) N-[(4-Chloro-7-quinolyl)carbonyl]ethanesulfonamide
^1H NMR (200MHz, DMSO-d_6) : δ 1.31 (t, J=7.4Hz, 3H), 3.58 (d, J=7.4Hz, 2H), 7.93 (d, J=4.7Hz, 1H), 8.19 (dd, J=8.8, 1.7Hz, 1H), 8.34 (d, J=8.8Hz, 1H), 8.73 (d, J=1.7Hz, 1H), 8.99 (d, J=4.7Hz, 1H)
MS m/z : 299 (MH^+)

(4) N-[(4-Chloro-7-quinolyl)carbonyl]-1-propanesulfonamide
^1H NMR (200MHz, DMSO-d_6) : δ 1.06 (t, J=7.4Hz, 3H), 1.70-1.88 (m, 2H), 3.57 (t, J=7.6Hz, 2H), 7.93 (d, J=4.7Hz, 1H), 8.19

(dd, J=8.8, 1.7Hz, 1H), 8.34 (d, J=8.8Hz, 1H), 8.73 (d, J=1.7Hz, 1H), 8.99 (d, J=4.7Hz, 1H)
MS m/z : 313 (MH^+)

(5) N-[(4-Chloro-7-quinolyl)carbonyl]-1-butanesulfonamide
MS (negative) m/z : 325 and 327 ($M-H^+$)

(6) N-[(4-Chloro-7-quinolyl)carbonyl]-1-pentanesulfonamide
MS (negative) m/z : 339 and 341 ($M-H^+$)

(7) N-[(4-Chloro-7-quinolyl)carbonyl]benzenesulfonamide
MS (negative) m/z : 345 and 347 ($M-H^+$)

(8) N-[(4-Chloro-7-quinolyl)carbonyl]-2-propanesulfonamide
MS (negative) m/z : 311 ($M-H^+$)

(9) N-[(4-Chloro-7-quinolyl)carbonyl]-1,1,1-trifluoromethanesulfonamide
MS (negative) m/z : 337 ($M-H^+$)

Preparation 32

To a solution of 4-[(2S)-2-(benzylamino)-3-hydroxypropyl]phenol (989 mg) in dimethyl sulfoxide (10 ml) was added potassium t-butoxide (431 mg) and the mixture was stirred at room temperature for 30 minutes. To the mixture was added 4-chloro-6-methoxyquinoline (744 mg) and the whole was heated at 100°C for 16 hours. After cooling to room temperature, the mixture was quenched by the addition of water (30 ml) and extracted with ethyl acetate (30 ml×1, 15 ml×1). The extracts were combined and washed with water (45 ml×2), brine (45 ml×1), dried over magnesium sulfate, and evaporated to give a brown paste (1.62 g). The crude product was chromatographed on 100 g of silica gel (eluent:

chloroform/methanol = 9/1) to give (2S)-2-(N-benzylamino)-3-[4-[(6-methoxy-4-quinolyl)oxy]phenyl]propan-1-ol (1.01 g) as a yellow gum.

MS m/z : 415 (MH^+)

Preparation 33

The following compounds were obtained in a manner similar to Preparation 29.

(1) 4-[2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenol

MS m/z : 382 and 384 (MH^+)

(2) 4-[(2S)-2-[N-Benzyl-N-[(2S)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl]amino]-3-hydroxypropyl]phenol

(+)APCI-MS m/z : 514 $(M+H)^+$

(3) 4-[(2S)-2-[N-Benzyl-N-[(2S)-3-(4-9H-carbazolyloxy)-2-hydroxypropyl]amino]-3-hydroxypropyl]phenol

(+)APCI-MS m/z : 497 $(M+H)^+$

(4) 4-[(2S)-2-[N-Benzyl-N-[(2S)-3-(4-fluorophenoxy)-2-hydroxypropyl]amino]-3-hydroxypropyl]phenol

(+)APCI-MS m/z : 426 $(M+H)^+$

(5) (S)-4-[2-[N-Benzyl-N-(2-hydroxy-3-phenoxypropyl)-amino]ethyl]phenol

(+)APCI-MS m/z : 378 $(M+H)^+$

Preparation 34

To a suspension of 4-hydroxy-8-quinolinecarboxylic acid (4.00 g) in thionyl chloride (40 ml) was added one drop of dimethyl formamide and the mixture was refluxed for 1 hour.

After cooling to room temperature, the excess thionyl chloride was removed by evaporation to give 4-chloro-8-quinolinecarbonyl chloride hydrochloride (5.8 g) as a yellow solid.

Preparation 35

To a suspension of 4-chloro-8-quinolinecarbonyl chloride hydrochloride (1.00 g) in dichloromethane (20 ml) were successively added dimethylamine hydrochloride (466 mg) and triethylamine (2.65 ml) at room temperature. The mixture was stirred at the same temperature for 14 hours. After evaporation of the solvent, the residue was partitioned between ethyl acetate (30 ml) and water (30 ml). The organic layer was separated, washed with water (30 ml×1), brine (30 ml×1), and then dried over magnesium sulfate. Filtration followed by evaporation gave an orange paste (528 mg). The crude product was purified by recycling preparative high pressure liquid chromatography equipped with a gel permeation chromatography column (chloroform) to give 4-chloro-N,N-dimethyl-8-quinolinecarboxamide (515 mg) as a yellow crystalline solid.

MS m/z : 234 and 236 (MH^+)

Preparation 36

The following compounds were obtained in a manner similar to Preparation 35.

(1) 4-Chloro-N-(2-hydroxyethyl)-8-quinolinecarboxamide

MS m/z : 251 and 253 (MH^+)

(2) 4-Chloro-N-ethyl-8-quinolinecarboxamide

(+)APCI-MS m/z : 235, 237 $(M+H)^+$

(3) 4-Chloro-N-ethyl-N-methyl-8-quinolinecarboxamide
(+)APCI-MS m/z : 249, 251 $(M+H)^+$

(4) 4-Chloro-N-(2,2,2-trifluoroethyl)-8-quinolinecarboxamide
(+)APCI-MS m/z : 289, 291 $(M+1)^+$

(5) tert-Butyl [N-[(4-chloro-8-quinolyl)carbonyl]amino]acetate
(+)ESI-MS m/z : 343, 345 $(M+Na)^+$

(6) tert-Butyl 3-[N-[(4-chloro-8-quinolyl)carbonyl]amino]-propanoate
(+)ESI-MS m/z : 357, 359 $(M+Na)^+$

(7) 4-Chloro-N-(2-hydroxyethyl)-8-quinolinecarboxamide
(+)ESI-MS m/z : 251, 253 $(M+H)^+$

Preparation 37

To a solution of 4-chloro-7-methoxyquinoline (1.00 g) in 1,2-dichloroethane (30 ml) was added a solution of boron tribromide in dichloromethane (1.0 M, 15.5 ml) at 5°C. After stirring at 5°C for 1 hour, the mixture was warmed to room temperature and stirred overnight. Furthermore, the mixture was warmed to 60°C and stirred for 15 hours. The solvent was removed by evaporation and the residue was partitioned between ethyl acetate (30 ml) and a saturated solution of sodium hydrogencarbonate in water (30 ml). The organic layer was separated and washed with brine (30 ml×1), dried over magnesium sulfate, filtered and evaporated to give a yellow solid (1.03 g). The solid was chromatographed on 15 g of silica gel (NH-DM1020, Fuji Silysia Chemical Ltd., chloroform : methanol = 9 : 1) to give 4-chloro-7-quinolinol (412 mg) as a yellow solid.
MS m/z : 180 and 182 (MH^+)

Preparation 38

To a suspension of 4-chloro-7-quinolinol (300 mg) in dimethyl formamide (6.0 ml) was added potassium t-butoxide (powdered, 277 mg) and the mixture was stirred at room temperature for 30 minutes. To the solution was added tert-butyl chloroacetate (287 μl) and the mixture was stirred at room temperature for 3 hours. The mixture was quenched by the addition of water (30 ml) and extracted with ethyl acetate (30 ml×1). The organic layer was separated and washed with water (30 ml×2), brine (30 ml×1), and dried over magnesium sulfate. Filtration followed by evaporation gave a yellow oil (463 mg). The oil was chromatographed on 25 g of silica gel (chloroform : methanol = 98 : 2) to give tert-butyl [(4-chloro-7-quinolyl)oxy]acetate (452 mg) as a pale-yellow oil. MS m/z : 294 and 296 (MH^+)

Preparation 39

To a suspension of 4-chloro-7-quinolinecarboxylic acid (600 mg) in dimethyl formamide (12.0 ml) were added successively tert-butyl 3-aminopropanoate hydrochloride (630 mg) and 1-hydroxybenzotriazole hydrate (469 mg). To the mixture was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (538 mg) at room temperature and the mixture was stirred for 20 hours. The reaction mixture was diluted with ethyl acetate (30 ml) and washed with water (30 ml×3), a saturated solution of sodium hydrogencarbonate in water (30 ml ×2), brine (30 ml×1), and dried over magnesium sulfate. Filtration followed by evaporation gave a pale-yellow foam (1.07 g). The crude product was purified by recycling preparative high pressure liquid chromatography equipped with a gel permeation chromatography column (chloroform) to give tert-butyl N-[(4-chloro-7-quinolyl)carbonyl]-beta-alaninate

(656 mg) as a white foam.

Preparation 40

To a solution of tert-butyl (4S)-4-(4-hydroxybenzyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (500 mg) in dimethyl sulfoxide (5.0 ml) was added potassium tert-butoxide (201 mg) and the mixture was stirred at room temperature for 1 hour. To the mixture was added tert-butyl N-[(4-chloro-7-quinolyl)carbonyl]-beta-alaninate (599 mg) and the whole was stirred at 100°C for 24 hours. The reaction mixture was quenched by the addition of water (30 ml) and extracted with ethyl acetate (30 ml×1). The extract was washed with water (30 ml×2), brine (30 ml×1), and dried over magnesium sulfate. Filtration followed by evaporation gave a yellow foam (843 mg). The crude product was purified by recycling preparative high pressure liquid chromatography equipped with a gel permeation chromatography column (eluent: chloroform) to give tert-butyl N-[[4-[4-[[(4S)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-(oxazolidine-4-yl)methyl]phenoxy]-7-quinolyl]-carbonyl]-beta-alaninate (460 mg) as a yellow foam..

MS m/z : 606 (MH^+), 628 ($M+Na^+$)

Preparation 41

Tert-butyl N-[[4-[4-[[(4S)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-(oxazolidine-4-yl)methyl]phenoxy]-7-quinolyl]-carbonyl]-beta-alaninate (437 mg) was dissolved in 4N hydrogen chloride in ethanol (10 ml) and the solution was stirred at room temperature overnight. The precipitates were collected by filtration, washed with a small portion of ethanol and dried under reduced pressure to give ethyl N-[[4-[4-[(2S)-2-amino-3-hydroxypropyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate dihydrochloride (268 mg) as a white powder.

MS m/z : 483 (MH^+)

Preparation 42

Under nitrogen, a suspension of 4-chloro-8-quinolinecarboxylic acid (400 mg) and thionyl chloride (3 ml) in the presence of one drop of N,N-dimethylformamide was refluxed for 30 minutes. The mixture was evaporated and dried under reduced pressure. Under nitrogen at 5°C, to a suspension of the above obtained compound in dichloromethane (20 ml) were added dimethylamine hydrochloride (190 mg) and triethylamine (1.4 ml), and the mixture was stirred at room temperature for 2 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1 to 1 : 10) to give 4-chloro-N,N-dimethyl-8-quinolinecarboxamide (300 mg).

(+)APCI-MS m/z : 235, 237 $(M+H)^+$

Preparation 43

Under nitrogen at room temperature, to a solution of ethyl 2-aminobenzoate (13 ml) in ethanol (40 ml) were added triethyl orthoformate (17 ml) and 2,2-dimethyl-1,3-dioxane-4,6-dione (14 g), and the mixture was stirred at 60°C for 1 hour. The resulting mixture was cooled to 5°C and to this one was added ethyl acetate (40 ml). After the mixture was being stirred at the same temperature for 1 hour, the precipitates were collected by filtration. The filter cake was washed with ethyl acetate and dried under reduced pressure to give ethyl 2-[N-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)-methyl]amino]benzoate (27 g).

(+)ESI-MS m/z : 342 $(M+Na)^+$

Preparation 44

Under nitrogen at 220°C, ethyl 2-[N-[(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methyl]amino]benzoate (27 g) was added to diphenyl ether (130 ml) by small portions, and the mixture was stirred at the same temperature for 1 hour. The resulting mixture was cooled to room temperature and to this one was added hexane (130 ml) dropwise. The precipitates were collected by filtration and the filter cake was washed with a mixture of hexane and ethyl acetate (5 : 1). The filter cake was dried under reduced pressure to gave ethyl 4-hydroxy-8-quinolinecarboxylate (12 g).
(+)APCI-MS m/z : 218 $(M+H)^+$

Preparation 45

A mixture of ethyl 4-hydroxy-8-quinolinecarboxylate (12 g) and 1N sodium hydroxide (280 ml) in 1,4-dioxane (280 ml) was refluxed for 17 hours. The resulting mixture was cooled to 5°C and to this one was added 1N hydrochloric acid (280 ml) dropwise. After stirring at the same temperature for 30 minutes, the precipitates were collected by filtration. The filter cake was washed with water and dried under reduced pressure to give 4-hydroxy-8-quinolinecarboxylic acid (10 g).
(+)APCI-MS m/z : 190 $(M+H)^+$

Preparation 46

4-Chloro-8-quinolinecarbonyl chloride hydrochloride was obtained in a manner similar to Preparation 34.

Preparation 47

Under nitrogen, a mixture of 3-nitroaniline (20 g) and diethyl ethoxymethylenemalonate (39 ml) was stirred at 100°C for 2 hours. The resulting mixture was evaporated under

reduced pressure to remove the liberated ethanol. To the residue was added diphenyl ether (200 ml), and the mixture was refluxed for 90 minutes. The resulting mixture was cooled to room temperature and stirred for 12 hours. The precipitates were collected by filtration and the filter cake was washed with a mixture of hexane and ethyl acetate (1 : 1), followed by drying to give ethyl 4-hydroxy-7-nitro-3-quinolinecarboxylate (12 g).

(+)ESI-MS m/z : 285 $(M+Na)^+$

Preparation 48

Ethyl 4-hydroxy-6-(trifluoromethyl)-3-quinolinecarboxylate was obtained in a manner similar to Preparation 47.

(+)APCI-MS m/z : 286 $(M+H)^+$

Preparation 49

A mixture of ethyl 4-hydroxy-7-nitro-3-quinolinecarboxylate (12 g) and sodium hydroxide (7.5 g) in water (75 ml) was refluxed for 1 hour. The resulting mixture was cooled to 5°C and to this one was added 1N hydrochloric acid (190 ml). The precipitates were collected by filtration and the filter cake was washed with water, followed by drying to give 4-hydroxy-7-nitro-3-quinolinecarboxylic acid (10 g).

(-)ESI-MS m/z : 233 $(M-H)^-$

Preparation 50

4-Hydroxy-6-(trifluoromethyl)-3-quinolinecarboxylic acid was obtained in a manner similar to Preparation 49.

(-)ESI-MS m/z : 256 $(M-H)^-$

Preparation 51

A mixture of 4-hydroxy-7-nitro-3-quinolinecarboxylic

acid (8.0 g) in diphenyl ether (80 ml) was refluxed for 1 hour. The resulting mixture was cooled to room temperature and to this one was added hexane (80 ml). After the mixture was stirred for 1 hour, the precipitates were collected by filtration and the filter cake was washed with a mixture of hexane and ethyl acetate (1 : 2), followed by drying, to give 7-nitro-4-quinolinol (6.2 g).
(+)APCI-MS m/z : 191 $(M+H)^+$

Preparation 52

6-(Trifluoromethyl)-4-quinolinol was obtained in a manner similar to Preparation 51.
(+)APCI-MS m/z : 214 $(M+H)^+$

Preparation 53

Under nitrogen, a mixture of 7-nitro-4-quinolinol (6.1 g) and phosphorus oxychloride (30 ml) was refluxed for 1 hour. The resulting mixture was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran and the solution was poured into 28% ammonium hydroxide and the mixture was cooled to 5°C. The aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure, followed by drying, to give 4-chloro-7-nitroquinoline (3.3 g).
(+)APCI-MS m/z : 209, 211 $(M+H)^+$

Preparation 54

4-Chloro-6-(trifluoromethyl)quinoline was obtained in a manner similar to Preparation 53.
(+)APCI-MS m/z : 232, 234 $(M+H)^+$

Preparation 55

A mixture of 4-(2-aminoethyl)phenol (20 g) and benzaldehyde (16 ml) in toluene (200 ml) in the presence of p-toluenesulfonic acid monohydrate (1.4 g) was refluxed for 2 hours to remove water as the toluene azeotrope. After removal of toluene by evaporation, to a solution of the residue in tetrahydrofuran (200 ml) was added dropwise sodium borohydride (6.1 g), followed by methanol (100 ml) under nitrogen at 5°C, and the mixture was stirred at room temperature for 3 hours. The resulting mixture was poured into ice-cold water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was triturated with a mixture of chloroform and hexane, followed by drying, to give 4-[2-(benzylamino)ethyl]phenol (20 g).

(+)APCI-MS m/z : 228 $(M+H)^+$

Preparation 56

At 5°C, to 4-chloro-6-(trifluoromethyl)quinoline (500 mg) was added 30% fuming sulfuric acid (2 ml) dropwise, and the mixture was stirred at 100°C for 7.5 hours. The resulting mixture was poured into ice-cold water carefully and the aqueous mixture was adjusted at pH 3.5 with concentrated hydrochloric acid. The precipitates were collected by filtration and the filter cake was washed successively with water and ethanol, followed by drying, to give 4-chloro-6-quinolinecarboxylic acid (420 mg).

(-)ESI-MS m/z : 206 $(M-H)^-$

Preparation 57

The following compounds were obtained in a manner similar to Preparation 42.

(1) 4-Chloro-N,N-dimethyl-6-quinolinecarboxamide
(+)ESI-MS m/z : 257, 259 $(M+Na)^+$

(2) 4-Chloro-N,N-dimethyl-2-quinolinecarboxamide
(+)APCI-MS m/z : 235, 237 $(M+H)^+$

(3) 4-Chloro-N,N-dimethyl-3-quinolinecarboxamide
(+)APCI-MS m/z : 235, 237 $(M+H)^+$

Preparation 58

4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenol was obtained in a manner similar to Example 43.
(+)APCI-MS m/z : 322, 324 $(M+H)^+$

Preparation 59

Under nitrogen at room temperature, to a solution of (S)-4-[4-[2-[N-benzyl-N-(2-hydroxy-3-phenoxypropyl)amino]-ethyl]phenoxy]-7-quinolinecarboxylic acid (1.0 g) in N,N-dimethylformamide (10 ml) were added imidazole (430 mg) and tert-butyldimethylsilyl chloride (820 mg), and the mixture was stirred at the same temperature for 24 hours. The resulting mixture was poured into buffer solution (pH 4) and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with buffer solution (pH 4) and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was dissolved in a mixture of methanol (15 ml), 1,4-dioxane (10 ml) and water (10 ml), and then to this one was added potassium carbonate (0.75 g). After stirring at room temperature for 20 minutes, 1N hydrochloric acid (5.5 ml) was added followed by concentration. The residue was poured into buffer solution (pH 4) and the aqueous mixture was extracted with ethyl acetate. The organic

layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced presssure. The residue was purified by column chromatography on silica gel (chloroform : methanol = 30 : 1 to 10 : 1) to give (S)-4-[4-[2-[N-benzyl-N-[2-[[tert-butyl(dimethyl)silyl]oxy]-3-phenoxypropyl]amino]ethyl]phenoxy]-7-quinolinecarboxylic acid (1.0 g).

(-)ESI-MS m/z : 661 $(M-H)^-$

Preparation 60

Under nitrogen at room temperature, to a solution of (S)-4-[4-[2-[N-benzyl-N-[2-[[tert-butyl(dimethyl)silyl]oxy]-3-phenoxypropyl]amino]ethyl]phenoxy]-7-quinolinecarboxylic acid (500 mg) in N,N-dimethylformamide (10 ml) was added 1,1'-carbonyldiimidazole (150 mg). After stirring at the same temperature, to this one were added n-propanesulfonamide (110 mg) and 1,8-diazabicyclo[4.3.0]undec-7-ene (0.14 ml), and the mixture was stirred at the same temperature for 4.5 hours. The resulting mixture was poured into buffer solution (pH 4) and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with buffer solution (pH 4) and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform : methanol = 50 : 1 to 10 : 1) to give (S)-N-[[4-[4-[2-[N-benzyl-N-[2-[[tert-butyl(dimethyl)silyl]oxy]-3-phenoxypropyl]amino]-ethyl]phenoxy]-7-quinolyl]carbonyl]-1-propanesulfonamide (520 mg).

(-)ESI-MS m/z : 767 $(M-H)^-$

Example 1

Under nitrogen, to a solution of 4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenol

(195 mg) and 4-chloroquinoline-7-carboxylic acid methylamide (127 mg) in dimethyl sulfoxide (5 ml) was added potassium tert-butoxide (64 mg) at room temperature, and the mixture was stirred at 100°C for 3 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (chloroform : methanol = 50 : 1 to 40 : 1) to give 4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-N-methyl-7-quinolinecarboxamide (124 mg).

^{1}H NMR (200MHz, $CDCl_3$) : δ 2.55-3.3 (9H, m), 3.5-4.05 (6H, m), 6.57 (1H, d, J=5.2Hz), 6.8-6.9 (2H, m), 6.95 (1H, t, J=7.3Hz), 7.10 (2H, d, J=8.5Hz), 7.2-7.4 (9H, m), 8.04 (1H, ABq, J=1.7, 8.7Hz), 8.38 (1H, d, J=1.4Hz), 8.44 (1H, d, J=8.7Hz), 8.69 (1H, d, J=5.2Hz)

Example 2

A mixture of 4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-N-methyl-7-quinolinecarboxamide (122 mg) and 10% palladium on activated carbon (50% wet, 50 mg) in methanol (5 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 2 hours. After filtration, the filtrate was evaporated under reduced pressure, followed by drying in vacuo, to give 4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-N-methyl-7-quinolinecarboxamide (80 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 2.6-3.8 (10H, m), 3.9-4.05 (2H, m), 4.05-4.3 (1H, m), 6.65 (1H, d, J=5.2Hz), 6.85-7.0 (3H, m), 7.2-7.55 (5H, m), 8.08 (1H, ABq, J=1.6, 8.7Hz), 8.37 (1H, d, J=8.7Hz), 8.52 (1H, m), 8.76 (1H, d, J=5.2Hz), 8.82 (1H, d,

J=4.6Hz)

Example 3

Under nitrogen, to a solution of 4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenol (336 mg) and 4-chloroquinoline-7-carboxylic acid dimethylamide (232 mg) in dimethyl sulfoxide (5 ml) was added potassium tert-butoxide (102 mg) at room temperature, and the mixture was stirred at 100°C for 1.5 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (chloroform: methanol = 50 : 1 to 20 : 1) to give 4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-7-quinolinecarboxamide (180 mg).

^{1}H NMR (200MHz, $CDCl_3$) : δ 2.6-3.3 (12H, m), 3.5-4.05 (6H, m), 6.56 (1H, d, J=5.2Hz), 6.8-6.9 (2H, m), 6.95 (1H, t, J=7.3Hz), 7.09 (2H, d, J=8.5Hz), 7.2-7.4 (9H, m), 7.64 (1H, ABq, J=1.6, 8.5Hz), 8.11 (1H, d, J=1.2Hz), 8.42 (1H, d, J=8.5Hz), 8.68 (1H, d, J=5.2Hz)

Example 4

A mixture of 4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-7-quinolinecarboxamide (171 mg) and 10% palladium on activated carbon (50% wet, 100 mg) in methanol (5 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 2 hours. After filtration, the filtrate was evaporated in vacuo, followed by trituration with hexane and drying in vacuo, to give 4-[4-[(2S)-3-hydroxy-2-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-N,N-dimethyl-7-

quinolinecarboxamide (115 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 2.8-3.8 (13H, m), 3.9-4.1 (2H, m), 4.15-4.3 (1H, m), 6.65 (1H, d, J=5.2Hz), 6.9-7.05 (3H, m), 7.2-7.4 (4H, m), 7.47 (2H, d, J=8.5Hz), 7.66 (1H, ABq, J=1.5, 8.5Hz), 8.02 (1H, d, J=1.2Hz), 8.35 (1H, d, J=8.5Hz), 8.74 (1H, d, J=5.2Hz)

Example 5

Under nitrogen, to a solution of 4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenol (100 mg) and N-(4-chloroquinoline-7-carbonyl)-methanesulfonamide (83.8 mg) in dimethyl sulfoxide (5 ml) was added potassium tert-butoxide (60.6 mg) at room temperature, and the mixture was stirred at 100°C for 3.5 hours. The resulting mixture was poured into a mixture of buffer solution (pH 4) and brine (1 : 1) and the aqueous mixture was extracted with dichloromethane five times. The combined organic layers were dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1 to 10 : 1) to give N-[4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]-3-hydroxypropyl]phenoxy]quinoline-7-carbonyl]-methanesulfonamide (44.8 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 2.6-4.0 (15H, m), 6.59 (1H, d, J=5.1 Hz), 6.8-6.95 (3H, m), 7.15-7.45 (11H, m), 8.15 (1H, ABq, J=1.6, 8.7Hz), 8.33 (1H, d, J=8.7Hz), 8.60 (1H, d, J=1.3Hz), 8.71 (1H, d, J=5.2Hz)

Example 6

A mixture of N-[4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-quinoline-7-carbonyl]methanesulfonamide (44.8 mg) and 10% palladium on activated carbon (50% wet; 40 mg) in methanol (5

ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 7 hours. After filtration, the filtrate was evaporated in vacuo, followed by trituration with diethyl ether, and drying in vacuo, to give N-[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]propyl]phenoxy]quinoline-7-carbonyl]methanesulfonamide (22 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 2.6-3.8 (10H, m), 3.9-4.0 (2H, m), 4.1-4.3 (1H, m), 6.59 (1H, d, J=5.1 Hz), 6.8-7.0 (3H, m), 7.1-7.5 (6H, m), 8.15-8.25 (2H, m), 8.55 (1H, s), 8.70 (1H, d, J=5.1Hz)

Example 7

Under nitrogen, to a solution of 4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenol (100 mg) and N-(4-chloroquinoline-7-carbonyl)methanesulfonamide (82.9 mg) in dimethyl sulfoxide (5 ml) was added potassium tert-butoxide (59.9 mg) at room temperature, and the mixture was stirred at 100°C for 3 hours. The resulting mixture was poured into a mixture of buffer solution (pH 4) and brine (1 : 1) and the aqueous mixture was extracted with dichloromethane five times. The combined organic layers were dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by thin layer silica gel chromatography (chloroform : methanol = 5 : 1) to give N-[4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-quinoline-7-carbonyl]methanesulfonamide (24.7 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 2.6-4.0 (12H, m), 4.95-5.0 (1H, m), 6.58 (1H, d, J=5.1Hz), 7.1-7.4 (13H, m), 8.16 (1H, ABq, J=1.5, 8.7Hz), 8.32 (1H, d, J=8.7Hz), 8.59 (1H, d, J=1.2Hz), 8.71 (1H, d, J=5.1Hz)

Example 8

A mixture of N-[4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-quinoline-7-carbonyl]methanesulfonamide (22.6 mg) and 10% palladium on activated carbon (50% wet, 20 mg) in a mixture of methanol (5 ml) and chlorobenzene (5 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 4 hours. After filtration, the filtrate was evaporated in vacuo, followed by trituration with diethyl ether and drying in vacuo to give N-[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]quinoline-7-carbonyl]methanesulfonamide dihydrochloride (17 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 2.4-3.9 (10H, m), 3.1-3.8 (3H, m), 6.79 (1H, d, J=5.3Hz), 7.2-7.6 (8H, m), 8.1-8.2 (1H, m), 8.48 (1H, d, J=8.8Hz), 8.68 (1H, s), 8.89 (1H, d, J=5.4Hz)

Example 9

Under nitrogen, to a solution of 4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenol (200 mg) in dimethyl sulfoxide (5 ml) was added potassium tert-butoxide (54 mg) at room temperature. After stirring at the same temperature for 30 minutes, to this one was added 4-chloroquinoline-7-carboxylic acid ethyl ester (114 mg) and the mixture was stirred at 100°C for 7 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform : methanol = 200 : 1 to 50 : 1) to give ethyl 4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-

2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarboxylate (113 mg).
(+) APCI-MS m/s : 611, 613 $(M+H)^+$

Example 10

A mixture of ethyl 4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarboxylate (109 mg) and 10% palladium on activated carbon (50% wet, 50 mg) in a mixture of ethanol (2 ml) and chlorobenzene (2 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 13 hours. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by thin layer silica gel chromatography (chloroform : methanol = 5 : 1) to give ethyl 4-[4-[(2S)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarboxylate (51 mg).
(+) APCI-MS m/s : 521, 523 $(M+H)^+$

Example 11

To a solution of ethyl 4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarboxylate (45.8 mg) in methanol (2 ml) was added aqueous 1N sodium hydroxide (262 μl) at room temperature, and the mixture was stirred at the same temperature for 24 hours. The mixture was evaporated under reduced pressure and dried in vacuo to give sodium 4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarboxylate (50 mg).
(-) ESI-MS m/s : 491, 493 $(M-Na)^-$

Example 12

Under nitrogen, to a solution of 4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-

hydroxypropyl]phenol (200 mg) in dimethyl sulfoxide (5 ml) was added potassium tert-butoxide (54 mg) at room temperature. After stirring at the same temperature for 30 minutes, to this one was added 4-chloro-7-quinolinecarboxamide (114 mg) and the mixture was stirred at 100°C for 7 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform : methanol = 50 : 1 to 20 : 1) to give 4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarboxamide (56.1 mg).
(+)APCI-MS m/s : 582, 584 $(M+H)^+$

Example 13

A mixture of 4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarboxamide (54.6 mg) and 10% palladium on activated carbon (50% wet, 30 mg) in a mixture of ethanol (2 ml) and chlorobenzene (2 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 6 hours. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by thin layer silica gel chromatography (chloroform : methanol = 5 : 1) to give 4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarboxamide (7 mg).
(+)APCI-MS m/s : 492 $(M+H)^+$

Example 14

Under nitrogen, to a solution of 4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenol (200 mg) and 4-chloroquinoline-8-carboxylic acid amide (122

mg) in dimethyl sulfoxide (10 ml) was added potassium tert-butoxide (60.6mg) at room temperature, and the mixture was stirred at 100°C for 140 minutes. The resulting mixture was poured into a mixture of water and ethyl acetate. After separation, the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (chloroform : methanol = 50 : 1 to 20 : 1) to give 4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-8-quinolinecarboxamide (174 mg).

^{1}H NMR (200MHz, $CDCl_3$) : δ 2.6-3.3 (7H, m), 3.5-4.1 (5H, m), 6.58 (1H, d, J=5.3Hz), 6.8-6.85 (2H, m), 6.9-7.0 (1H, m), 7.05-7.15 (2H, m), 7.2-7.4 (9H, m), 7.65-7.75 (1H, m), 8.60 (1H, ABq, J=1.6, 8.3Hz), 8.66 (1H, d, J=5.3Hz), 8.90 (1H, ABq, J=1.6, 7.4Hz)

Example 15

A mixture of 4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-8-quinolinecarboxamide (160 mg) and 10% palladium on activated carbon (50% wet, 50 mg) in methanol (5 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 3 hours. After filtration, the filtrate was evaporated and dried in vacuo to give 4-[4-[(2S)-3-hydroxy-2-[[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-8-quinolinecarboxamide (100 mg).

^{1}H NMR (200MHz, DMSO-d_6) : δ 2.6-3.7 (7H, m), 3.9-4.2 (3H, m), 6.69 (1H, d, J=5.3Hz), 6.9-7.0 (3H, m), 7.2-7.4 (4H, m), 7.44 (2H, d, J=8.5Hz), 7.79 (1H, t, J=8.2Hz), 8.55 (1H, ABq, J=1.6, 8.3Hz), 8.65 (1H, ABq, J=1.6, 7.3Hz), 8.80 (1H, d, J=5.3Hz)

Example 16

Under nitrogen, a mixture of (2S)-2-benzylamino-3-[4-

(phenylamino)phenyl]propan-1-ol(100 mg) and (2S)-3-phenoxy-1,2-epoxypropane (45.2 mg) in ethanol (10 ml) was refluxed for 24 hours. An additional (2S)-3-phenoxy-1,2-epoxypropane (22.6 mg) was added and the mixture was refluxed for an another 20 hours. The mixture was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane : ethyl acetate =4 : 1 to 2 : 1) to give (2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-(phenylamino)phenyl]propan-1-ol (114 mg).

(+) APCI-MS m/s : 483 $(M+H)^+$

Example 17

A mixture of (2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-(phenylamino)phenyl]propan-1-ol (108 mg) and 10% palladium on activated carbon (50% wet, 50 mg) in methanol (5 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 3 hours. After filtration, the filtrate was evaporated and drying in vacuo to give (2S)-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]-3-[4-(phenylamino)phenyl]propan-1-ol (65 mg).

(+) APCI-MS m/s : 393 $(M+H)^+$

Example 18

Under nitrogen, a mixture of (2S)-2-benzylamino-3-[4-(phenylamino)phenyl]propan-1-ol (244 mg) and (2R)-2-(4-benzyloxy-3-nitrophenyl)oxirane (199 mg) in ethanol (10 ml) was refluxed for 24 hours. An additional (2R)-2-(4-benzyloxy-3-nitrophenyl)oxirane (99.5 mg) was added and refluxed for an another 22 hours. The mixture was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane : chloroform : ethyl acetate = 5 : 5 : 3 to 5 : 5 : 4) to give (2S)-2-[N-benzyl-N-[(2R)-2-(4-benzyloxy-3-nitrophenyl)-2-hydroxyethyl]amino]-3-[4-(phenylamino)-

phenyl]propan-1-ol (305 mg).
(+) APCI-MS m/s : 604 $(M+H)^+$

Example 19

To a solution of (2S)-2-[N-benzyl-N-[(2R)-2-(4-benzyloxy-3-nitrophenyl)-2-hydroxyethyl]amino]-3-[4-(phenylamino)phenyl]propan-1-ol (294 mg) in a mixture of ethanol (6 ml) and water (2 ml) were added powdered iron (81.6 mg) and ammonium chloride (13 mg) at room temperature, and the mixture was refluxed for 2 hours. Insoluble materials were filtered off. The filtrate was evaporated and dried in vacuo to give (2S)-2-[N-[(2R)-2-(3-amino-4-benzyloxyphenyl)-2-hydroxyethyl]-N-benzylamino]-3-[4-(phenylamino)phenyl]propan-1-ol (300 mg).
^{1}H NMR (200MHz, $CDCl_3$) : δ 2.45-2.6 (1H, m), 2.75-3.25 (4H, m), 3.5-3.6 (2H, m), 3.7-4.05 (2H, m), 4.4-4.55 (1H, m), 5.06 (2H, s), 6.5-7.5 (22H, m)

Example 20

Under nitrogen, a solution of (2S)-2-[N-[(2R)-2-(3-amino-4-benzyloxyphenyl)-2-hydroxyethyl]-N-benzylamino]-3-[4-(phenylamino)phenyl]propan-1-ol (150 mg), methanesulfonyl chloride (22.3 μl) and pyridine (31.7 μl) in a mixture of dichloromethane (5 ml) and N,N-dimethylformamide (2 ml) was stirred at 5°C for 2 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform : ethyl acetate = 10 : 1 to 1 : 1) to give N-[5-[(1R)-2-[N-benzyl-N-[(1S)-2-hydroxy-1-[4-(phenylamino)benzyl]ethyl]amino]-1-hydroxyethyl]-2-benzyloxyphenyl]methanesulfonamide (25.6 mg).

(+) ESI-MS m/s : 652 $(M+H)^+$

Example 21

A mixture of N-[5-[(1R)-2-[N-benzyl-N-[(1S)-2-hydroxy-1-[4-(phenylamino)benzyl]ethyl]amino]-1-hydroxyethyl]-2-benzyloxyphenyl]methanesulfonamide (22.5 mg) and 10% palladium on activated carbon (50% wet, 10 mg) in methanol (3 ml) was stirred at room temperature in the presence of hydrogen at an atmospheric pressure for 2 hours. After filtration, the filtrate was evaporated under reduced pressure, triturated with hexane and dried in vacuo to give N-[2-hydroxy-5-[(1R)-1-hydroxy-2-[N-[(1S)-2-hydroxy-1-[4-(phenylamino)benzyl]ethyl]amino]ethyl]phenyl]methanesulfonamide (13 mg).

(+) APCI-MS m/s : 472 $(M+H)^+$

Example 22

Under nitrogen, to a solution of (2S)-2-amino-4-[4-(4-quinolinyloxy)phenyl]butan-1-ol dihydrochloride (226 mg) in ethanol (5 ml) was added sodium methoxide (28% in methanol, 0.24 ml) at 5°C. After stirring at room temperature for 15 minutes, to this one was added (2S)-3-phenoxy-1,2-epoxypropane (97.9 mg), and the mixture was refluxed for 6 hours. An additional (2S)-3-phenoxy-1,2-epoxypropane (100 mg) was added and the mixture was refluxed for an another 22 hours. Insoluble materials were removed by filtration. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1 to 10 : 1) to give (2S)-2-[[(2S)-2-hydroxy-3-phenoxypropyl]amino]-4-[4-(4-quinolinyloxy)phenyl]butan-1-ol (53 mg).

(+)ESI-MS m/s : 459 $(M+H)^+$

Example 23

To a solution of 4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenol (200 mg) in dimethyl sulfoxide (4.0 ml) was added potassium tert-butoxide (55.1 mg) and the mixture was stirred at room temperature for 30 minutes. To the mixture was added 1-chlorophthalazine (105 mg) and the whole was stirred at 100°C for 8 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 ml) and washed successively with water (20 ml×2) and brine (20 ml×1), and dried over magnesium sulfate. Filtration followed by evaporation gave a yellow foam (252 mg). The crude product was purified by preparative recycling high pressure liquid chromatography using a gel permeation chromatography column (eluent : chloroform) to give (2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-(1-phthalazinyloxy)phenyl]propan-1-ol (80.0 mg) as a yellow foam.

MS m/z : 536 (MH^+)

^1H NMR (200MHz, $CDCl_3$) : δ 2.55-3.21 (m, 7H), 3.59-4.01 (m, 7H), 6.74-6.98 (m, 3H), 7.23-7.33 (m, 11H), 7.95-7.99 (m, 3H), 8.40-8.44 (m, 1H), 9.25 (s, 1H)

Example 24

The following compounds were obtained in a manner similar to Example 23.

(1) (2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-[(7-fluoro-4-quinolyl)oxy]phenyl]propan-1-ol

MS m/z : 553 (MH^+)

(2) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-methoxy-3-quinolinecarboxamide

MS m/z : 608 (MH^+)

^{1}H NMR (200MHz, $CDCl_3$) : δ 2.46-3.10 (m, 7H), 3.45-3.91 (m, 7H), 3.96 (s, 3H, OMe), 5.74 (br, 1H), 6.74-7.30 (m, 16H), 7.50 (d, J=2.5Hz, 1H), 7.74 (d, J=9.2Hz, 1H), 9.53 (s, 1H)

(3) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-fluoro-3-quinolinecarboxamide

MS m/z : 596 (MH^+)

^{1}H NMR (200MHz, $CDCl_3$) : δ 2.48-3.12 (m, 7H), 3.49-3.95 (m, 7H), 6.76-7.30 (m, 2H), 8.16-8.24 (m, 1H), 9.52 (s, 1H)

(4) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]-3-hydroxypropyl]phenoxy]-3-quinolinecarboxamide

MS m/z : 578 (MH^+)

^{1}H NMR ($CDCl_3$, 200MHz) : δ 2.47-3.19 (m, 7H), 3.45-3.94 (m, 7H), 5.87 (br, 1H), 6.76-7.08 (m, 8H), 7.22-7.30 (m, 7H), 7.45-7.53 (m, 1H), 7.74-7.90 (m, 2H), 8.20 (d, J=8.3Hz, 1H), 9.59 (s, 1H)

(5) (2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-[(6-methoxy-4-quinolyl)oxy]phenyl]propan-1-ol

MS m/z : 565 (MH^+)

^{1}H NMR (200MHz, $CDCl_3$) : δ 2.53-3.22 (m, 7H), 3.59-4.00 (m, 7H), 3.97 (s, 3H), 6.51 (d, J=5.2Hz, 1H), 6.76-7.34 (m, 14H), 7.40 (dd, J=2.8, 9.2Hz, 1H), 7.59 (d, J=2.8Hz, 1H), 7.99 (d, J=9.2Hz, 1H), 8.52 (d, J=5.2Hz, 1H)

(6) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]-3-hydroxypropyl]phenoxy]-6-methoxy-3-quinolinecarboxamide

MS m/z : 608 (MH^+)

^{1}H NMR (200MHz, $CDCl_3$) : δ 2.48-3.11 (m, 7H), 3.45-3.65 (m, 3H), 3.71 (s, 3H), 3.78-3.94 (m, 4H), 5.86 (br, 1H), 6.74-6.84

(m, 4H), 6.91-7.09 (m, 5H), 7.22-7.30 (m, 6H), 7.42 (dd, J=2.8, 9.2Hz, 1H), 8.08 (d, J=9.2Hz, 1H), 9.41 (s, 1H)

(7) (2S)-2-[N-[(2S)-2-Hydroxy-3-phenoxypropyl]amino]-3-[4-(4-quinazolinyloxy)phenyl]propan-1-ol
MS m/z : 446 (MH^+)
^1H NMR (200MHz, DMSO-d_6) : δ 2.70-2.83 (m, 5H), 3.24-3.54 (m, 3H), 3.85-3.96 (m, 3H), 4.64 (br, 1H), 5.01 (br, 1H), 6.87-6.95 (m, 3H), 7.19-7.35 (m, 6H), 7.75-7.83 (m, 1H), 7.98-8.10 (m, 2H), 8.32-8.40 (m, 1H), 8.71 (s, 1H)
IR (KBr) : 3381, 2925, 1622, 1576, 1493, 1385, 1246, 1213 cm^{-1}

(8) (2S)-2-[N-Benzyl-N-[(2R)-2-[4-(benzyloxy)-3-nitrophenyl]-2-hydroxyethyl]amino]-3-[4-[[7-(trifluoromethyl)-4-quinolyl]oxy]phenyl]propan-1-ol
MS m/z : 724 (MH^+)

(9) (2S)-2-[N-Benzyl-N-[(2R)-2-[4-(benzyloxy)-3-nitrophenyl]-2-hydroxyethyl]amino]-3-[4-[(7-methoxy-4-quinolyl)oxy]phenyl]-propan-1-ol
MS m/z : 686 (MH^+)

(10) (2S)-2-[N-Benzyl-N-[(2R)-2-[4-(benzyloxy)-3-nitrophenyl]-2-hydroxyethyl]amino]-3-[4-[(7-fluoro-4-quinolyl)oxy]phenyl]-propan-1-ol

(11) 4-[4-[(2S)-2-[[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenoxy]-3-quinolinecarboxamide
MS m/z : 492 (MH^+)
^1H NMR (200MHz, DMSO-d_6) : δ 1.85 (br, 1H), 2.41-2.69 (m, 5H), 3.12-3.33 (m, 2H), 4.52 (br, 2H), 5.37 (d, J=4.1Hz, 1H), 6.77 (d, J=8.5Hz, 2H), 7.09 (d, J=8.5Hz, 2H), 7.17-7.37 (m, 4H), 7.56-7.64 (m, 2H), 7.81-7.93 (m, 3H), 8.13 (d, J=8.4Hz, 1H),

9.08 (s, 1H)

IR (KBr) : 3392, 1662, 1618, 1498, 1429, 1211, 1093, 771 cm^{-1}

Example 25

To a solution of (2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-(1-phthalazinyloxy)phenyl]propan-1-ol (74.3 mg) in methanol (3.0 ml) was added 10% palladium on activated carbon (50% wet, 74 mg) and the solution was hydrogenated at room temperature for 6 hours. The mixture was filtered, washed with methanol, and concentrated in vacuo to give a pale-yellow paste (45.3 mg). The crude product was purified by preparative recycling high pressure liquid chromatography using a gel permeation chromatography column (eluent : chloroform) to give (2S)-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-(1-phthalazinyloxy)phenyl]propan-1-ol (16.2 mg) as a white powder.

MS m/z : 446(MH^+)

^1H NMR (200MHz, $CDCl_3$) : δ 2.72-4.70 (m, 13H), 6.78-7.44 (m, 14H), 7.93-7.95 (m, 3H), 8.34-8.37 (m, 1H), 9.21 (s, 1H)

Example 26

The following compounds were obtained in a manner similar to Example 25.

(1) (2S)-3-[4-[(7-Fluoro-4-quinolyl)oxy]phenyl]-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propan-1-ol

MS m/z : 463 (MH^+)

^1H NMR (200MHz, $CDCl_3$) : δ 3.06-4.14 (m, 12 H), 4.64 (br, 1 H), 6.45 (d, J=5.2Hz, 1H), 6.74-7.39 (m, 10 H), 7.70 (dd, J=2.4, 10.1Hz, 1H), 8.31 (dd, J=6.1, 9.2Hz, 1H), 8.60 (d, J=5.2Hz, 1H)

IR (KBr) : 3381, 1630, 1581, 1500, 1429, 1244, 1223 cm^{-1}

(2) 4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-methoxy-3-quinolinecarboxamide

MS m/z : 518 (MH^+)

^1H NMR (200MHz, DMSO-d_6) : δ 2.55-2.83 (m, 5H), 3.21 (br, 2H), 3.82-3.91 (m, 3H), 3.94 (s, 3H, OMe), 4.61 (br, 1H), 5.03 (br, 1H), 6.75 (d, J=8.6Hz, 2H), 6.85-6.92 (m, 3H), 7.13 (d, J=8.6Hz, 2H), 7.21-7.28 (m, 3H), 7.50 (d, J=2.5Hz, 1H), 7.62 (br, 1H), 7.76-7.80 (br, 1H), 9.03 (s, 1H)

IR (KBr) : 3410, 3186, 2927, 1658(C=O), 1614, 1498, 1423, 1247, 1221, 754 cm^{-1}

(3) 7-Fluoro-4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-3-quinolinecarboxamide

MS m/z : 506 (MH^+)

^1H NMR (200MHz, DMSO-d_6) : δ 2.61-3.42 (m, 8H), 3.90 (br, 3H), 4.78 (br, 1H), 5.21 (br, 1H), 6.79-6.93 (m, 5H), 7.15-7.29 (m, 4H), 7.57 (dd, J=2.9, 9.3Hz, 1H), 7.72 (br, 1H), 7.81 (dd, J=2.9, 8.7Hz, 1H), 7.93 (br, 1H), 8.22 (dd, J=5.3, 9.3Hz, 1H), 9.04 (s, 1H)

IR (KBr) : 3388, 3232, 2922, 1662, 1603, 1500, 1435, 1245, 1207 cm^{-1}

(4) (2S)-2-[N-[(2S)-2-Hydroxy-3-phenoxypropyl]amino]-3-[4-[(6-methoxy-4-quinolyl)oxy]phenyl]propan-1-ol

MS m/z : 475 (MH^+)

^1H NMR (200MHz, DMSO-d_6) : δ 2.62-2.89 (m, 5H), 3.15-3.50 (m, 3H), 3.81-3.95 (m, 6H), 4.66 (br, 1H), 5.00 (br, 1H), 6.53 (d, J=5.1Hz, 1H), 6.86-6.97 (m, 3H), 7.14-7.38 (m, 6H), 7.46 (dd, J=2.8, 9.2Hz, 1H), 7.56 (d, J=2.8Hz, 1H), 7.70 (d, J=9.2Hz, 1H), 8.50 (d, J=5.1Hz, 1H)

IR (KBr) : 3425, 1626, 1595, 1504, 1471, 1238, 1217, 1032, 839, 754 cm^{-1}

(5) 4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-6-methoxy-3-quinolinecarboxamide

MS m/z : 518 (MH^+)

^1H NMR (200MHz, DMSO-d_6) : δ 1.83 (br, 1H), 2.57-2.76 (m, 5H), 3.16-3.22 (m, 2H), 3.70 (s, 3H, OMe), 3.80-3.92 (m, 3H), 4.52 (brt, J=4.9Hz, 1H), 4.93 (brd, J=4.0Hz, 1H), 6.77-6.91 (m, 5H), 7.11-7.27 (m, 5H), 7.49 (dd, J=2.8, 9.2Hz, 1H), 7.66 (br, 1H), 7.84 (br, 1H), 8.04 (d, J=9.2Hz, 1H) 8.90 (s, 1H)

IR (KBr) : 3398, 3215, 2941, 1662, 1620, 1599, 1502, 1425, 1246, 1209 cm^{-1}

(6) N-[2-Hydroxy-5-[(1R)-1-hydroxy-2-[N-[(1S)-2-hydroxy-1-[4-[N-[7-(trifluoromethyl)-4-quinolyl]oxy]benzyl]ethyl]-amino]ethyl]phenyl]methanesulfonamide

MS m/z : 592 (MH^+)

IR (KBr) : 3267, 1599, 1576, 1502, 1329, 1302, 1211, 1155, 1126 cm^{-1}

(7) N-[2-Hydroxy-5-[(1R)-1-hydroxy-2-[N-[(1S)-2-hydroxy-1-[4-[(7-methoxy-4-quinolyl)oxy]benzyl]ethyl]amino]ethyl]phenyl]-methanesulfonamide

MS m/z : 554 (MH^+)

IR (KBr) 3423, 1622, 1506, 1446, 1429, 1315, 1228, 1151 cm^{-1}

(8) N-[5-[(1R)-2-[N-[(1S)-1-[4-[(7-Fluoro-4-quinolyl)oxy]benzyl]-2-hydroxyethyl]amino]-1-hydroxyethyl]-2-hydroxyphenyl]methanesulfonamide

MS m/z : 542 (MH^+)

^1H NMR (200MHz, $CDCl_3$) : δ 2.78-3.77 (m, 11H), 4.89 (br, 1H), 5.45 (br, 1H), 6.11 (br, 1H), 6.57 (d, J=5.2Hz, 1H), 6.93 (d, J=8.4Hz, 1H), 7.10 (d, J=8.4Hz, 1H), 7.27-7.31 (m, 2H), 7.46

(d, J=8.4Hz, 1H), 7.54-7.65 (m, 1H), 7.79 (dd, J=2.5, 10.5, 1H), 8.39 (dd, J=6.3, 9.2Hz, 1H), 8.71 (d, J =5.2Hz, 1H), 8.80 (br, 1H), 9.14 (br, 1H), 10.0 (br, 1H)

IR (KBr) : 3381, 1630, 1581, 1506, 1431, 1309, 1223, 1151 cm^{-1}

Example 27

To a suspension of 4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-3-quinolinecarboxamide (204 mg) in methanol (6.0 ml) was added 10% palladium on activated carbon (50% wet, 102 mg) and the mixture was hydrogenated at 1 atm for 30 minutes. To the reaction mixture was added 6.0 ml of tetrahydrofuran and the whole was further hydrogenated at 1 atm for 3 hours. The mixture was filtered, washed with methanol, and concentrated in vacuo to give a yellow foam (99.1 mg). The crude product was chromatographed on 10 g of silica gel (eluent : chloroform/methanol = 4/1) to give 4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-3-quinolinecarboxamide (84.9 mg) as a yellow foam.

MS m/z : 488 (MH^+)

^1H NMR (200MHz, DMSO-d_6) : δ 2.55-2.83 (m, 5H), 3.41 (br, 2H), 3.91 (br, 3H), 4.81 (br, 1H), 5.25 (br, 1H), 6.77-6.93 (m, 5H), 7.14-7.30 (m, 4H), 7.57-7.65 (m, 1H),7.70 (br, 1H), 7.81-7.93 (m, 3H), 8.13 (d, J=8.3Hz, 1H), 9.07 (s, 1H)

IR (KBr) : 3388, 3296, 3219, 1664, 1599, 1496, 1429, 1381, 1246, 1211 cm^{-1}

Example 28

To a solution of (2S)-2-[N-benzyl-N-[(2R)-2-[4-(benzyloxy)-3-nitrophenyl]-2-hydroxyethyl]amino]-3-[4-[[7-(trifluoromethyl)-4-quinolyl]oxy]phenyl]propan-1-ol (238 mg) in a mixed solvent of ethanol (9 ml) and water (3 ml) were added successively iron powder (55.1 mg) and ammonium chloride

(8.8 mg) at room temperature. The mixture was refluxed for 1 hour. After cooling to room temperature, the metal was removed by filtration and the filtrate was concentrated in vacuo. To the residue was added a saturated aqueous sodium hydrogencarbonate solution (20 ml) and the mixture was extracted with ethyl acetate (20 ml×1). The extract was washed successively with water (20 ml×1) and brine (20 ml×1), dried over magnesium sulfate, and evaporated to give (2S)-2-[N-[(2R)-2-[3-amino-4-(benzyloxy)phenyl]-2-hydroxyethyl]-N-benzylamino]-3-[4-[[7-(trifluoromethyl)-4-quinolyl]oxy]-phenyl]propan-1-ol (216 mg) as a pale-yellow foam.
MS m/z : 694 (MH^+)

Example 29

To a solution of (2S)-2-[N-[(2R)-2-[3-amino-4-(benzyloxy)phenyl]-2-hydroxyethyl]-N-benzylamino]-3-[4-[[7-(trifluoromethyl)-4-quinolyl]oxy]phenyl]propan-1-ol (100 mg) in dichloromethane (2.0 ml) were added successively pyridine (23.3 μl) and methanesulfonyl chloride (13.4 μl) at 0°C. After stirring for 1 hour, additional methanesulfonyl chloride (8.9 μl) was added. The reaction mixture was stirred at 0°C for 2 hours. The mixture was diluted with ethyl acetate (10 ml), washed successively with water (10 ml×1) and brine (10 ml×1). The organic solution was dried over magnesium sulfate, filtered, and evaporated to give a yellow foam (132 mg). The crude product was purified by preparative recycling high pressure liquid chromatography using a gel permeation chromatography column (eluent : chloroform/triethylamine = 99.5/0.5) to give N-[5-[(1R)-2-[N-benzyl-N-[(1S)-2-hydroxy-1-[4-[[7-(trifluoromethyl)-4-quinolyl]oxy]benzyl]ethyl]amino]-1-hydroxyethyl]-2-(benzyloxy)phenyl]methanesulfonamide (96.3 mg) as a white foam.

Example 30

The following compounds were obtained in a manner similar to Example 28.

(1) (2S)-2-[N-[(2R)-2-[3-Amino-4-(benzyloxy)phenyl]-2-hydroxyethyl]-N-benzylamino]-3-[4-[[7-methoxy-4-quinolyl]-oxy]phenyl]propan-1-ol

(2) (2S)-2-[N-[(2R)-2-[3-Amino-4-(benzyloxy)phenyl]-2-hydroxyethyl]-N-benzylamino]-3-[4-[(7-fluoro-4-quinolyl)oxy]-phenyl]propan-1-ol

Example 31

The following compounds were obtained in a manner similar to Example 29.

(1) N-[5-[(1R)-2-[N-Benzyl-N-[(1S)-2-hydroxy-1-[4-[(7-methoxy-4-quinolyl)oxy]benzyl]ethyl]amino]-1-hydroxyethyl]-2-(benzyloxy)phenyl]methanesulfonamide

(2) N-[5-[(1R)-2-[N-Benzyl-N-[(1S)-1-[4-[(7-fluoro-4-quinolyl)oxy]benzyl]-2-hydroxyethyl]amino]-1-hydroxyethyl]-2-(benzyloxy)phenyl]methanesulfonamide
MS m/z : 722 (MH^+)

Example 32

Potassium hydroxide powder (85% purity, 22.9 mg) was added to dimethyl sulfoxide (2.0 ml) at room temperature and the mixture was stirred at the same temperature for 1 hour. To the mixture was added 4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenol (100 mg) and stirred for 10 minutes. Further, 4-chloro-7-(trifluoromethyl)quinoline (73.3 mg) was added and the mixture

was stirred at 100°C for 5 hours. After cooling to room temperature, the mixture was diluted with ethyl acetate (10 ml) and washed successively with water (10 ml×2) and brine (10 ml×1), dried (magnesium sulfate), then evaporated to give a pale-brown solid (157 mg). The crude solid was purified by recycling preparative HPLC equipped with a GPC column (chloroform : triethylamine = 95.5/0.5) to give (2S)-2-[N-[(2S)-2-hydroxy-3-(phenoxy)propyl]amino]-3-[4-[7-(trifluoromethyl)-4-quinolyloxy]phenyl]propan-1-ol (51.4 mg) as a pale-yellow solid.

MS m/z : 513 (MH^+)

^1H NMR (200MHz, $CDCl_3$) : δ 1.99 (br, 3H), 2.77-3.03 (m, 5H), 3.47 (dd, J=5.1, 10.8Hz, 1H), 3.71 (dd, J=3.7, 10.8Hz, 1H), 3.99-4.05 (m, 3H), 6.63 (d, J=5.2Hz, 1H), 6.89-7.35 (m, 9H), 7.75 (d, J=8.8Hz, 1H), 8.40 (s, 1H), 8.50 (d, J=8.8Hz, 1H), 8.73 (d, J=5.2Hz, 1H)

Example 33

The following compounds were obtained in a manner similar to Example 32.

(1) (2S)-2-[N-[(2S)-2-Hydroxy-3-(phenoxy)propyl]amino]-3-[4-[8-(trifluoromethyl)-4-quinolyloxy]phenyl]propan-1-ol

MS m/z : 513 (MH^+)

^1H NMR (200MHz, $CDCl_3$) : δ 1.93 (br, 3H), 2.74-3.04 (m, 5H), 3.46 (dd, J=5.1, 10.8Hz, 1H), 3.70 (d, J=3.7, 10.8Hz, 1H), 4.00-4.08 (m, 3H), 6.64 (d, J=5.2Hz, 1H), 6.89-7.00 (m, 3H), 7.12 (d, J=6.6Hz, 2H), 7.25-7.35 (m, 4H), 7.59-7.67 (m, 1H), 8.13 (d, J=7.0Hz, 1H), 8.60 (d, J=7.5Hz, 1H), 8.82 (d, J=5.2Hz, 1H)

IR (KBr) : 3419, 2927, 1587, 1498, 1296, 1136 cm^{-1}

(2) (2S)-3-[4-[2,8-bis(Trifluoromethyl)-4-quinolyloxy]phenyl]-2-[N-[(2S)-2-hydroxy-3-(phenoxy)propyl]amino]propan-1-ol

MS m/z : 581 (MH^+)

^1H NMR (200MHz, $CDCl_3$) : δ 1.81 (br, 3H), 2.78-3.03 (m, 5H), 3.49 (dd, J=5.0, 10.9Hz, 1H), 3.71 (dd, J=3.7, 10.9Hz, 1H), 3.99-4.05 (m, 3H), 6.89-7.00 (m, 4H), 7.11-7.39 (m, 6H), 7.74 (t-like, J=7.9Hz, 1H), 8.21 (d, J=6.8Hz, 1H), 8.63 (d, J=8.4Hz, 1H)

IR (KBr) : 3423, 1593, 1500, 1317, 1138cm^{-1}

Example 34

A mixture of trifluoromethanesulfonic acid 4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]-N-benzylamino]propyl]phenyl ester (100 mg), 2-methoxyphenylboric acid (42.3 mg), triethylamine (56.3 mg), tetrakis(triphenylphosphine)-palladium (6.43 mg) and dimethylformamide (2 ml) was stirred at 90°C for 2 hours. The resulting mixture was added to saturated aqueous sodium hydrogencarbonate and ethyl acetate and partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 1 : 1) to give (2S)-3-[4-(2-methoxyphenyl)phenyl]-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propan-1-ol (50 mg) as a colorless foam.

MS m/z : 408 (M+1)

^1H NMR (200MHz, $CDCl_3$) : δ 3.05-3.20 (1 H, m), 3.25-4.05 (12H, m), 4.50-4.60 (1H, br-s), 6.80-7.40 (13H, m)

IR (KBr) : 3500-3200, 1606, 1650, 1587, 1246 cm^{-1}

Example 35

To a solution of (2S)-1-[N-benzyl-N-[2-(4-aminophenyl)-ethyl]amino]-3-phenoxypropan-2-ol (300 mg) in ethanol (8.0 ml) was added 4-chloro-7-methoxyquinoline (185 mg) and the mixture was refluxed for 11 hours. After cooling to room temperature,

the solvent was removed by evaporation to give a yellow foam (467 mg). The crude product was purified by recycling preparative high pressure liquid chromatography equipped with a gel permeation chromatography column (chloroform) to give (2S)-1-[N-benzyl-N-[2-[4-[(7-methoxy-4-quinolyl)amino]-phenyl]ethyl]amino]-3-phenoxypropan-2-ol (159 mg).

MS m/z : 534 (MH^+)

^1H NMR (200 MHz, $CDCl_3$): δ 2.68-2.95 (m, 6H), 3.69 (d, J=13.5Hz, 1H), 3.81 (s, 3H), 3.90 (s, 2H), 3.91 (d, J=13.5Hz, 1H), 3.99-4.08 (m, 1H), 6.52 (d, J=6.9Hz, 1H), 6.74-7.39 (m, 17H), 7.82 (d, J=6.9Hz, 1H), 8.55 (d, J=9.4Hz, 1H), 9.99 (br, 1H)

Example 36

The following compounds were obtained in a manner similar to Example 35.

(1) 4-[[4-[2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]ethyl]phenyl]amino]-7-quinolinecarboxamide

MS m/z : 547 (MH^+)

(2) (2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-[(7-methoxy-4-quinolyl)amino]phenyl]propan-1-ol

MS m/z : 564 (MH^+)

Example 37

To a solution of (2S)-1-[N-benzyl-N-[2-[4-[(7-methoxy-4-quinolyl)amino]phenyl]ethyl]amino]-3-phenoxypropan-2-ol (153 mg) in methanol (6.0 ml) was added 10% palladium on activated carbon (50% wet, 77 mg) and the mixture was hydrogenated at 1 atm for 2 hours. The catalyst was filtered off and the filtrate was concentrated in vacuo to give (2S)-1-[N-[2-[4-[(7-methoxy-4-quinolyl)amino]phenyl]ethyl]amino]-3-

phenoxypropan-2-ol (125 mg) as a yellow solid.
MS m/z : 444 (MH^+)
^1H NMR (200 MHz, $CDCl_3$) : δ 3.00-3.45 (m, 6H), 3.97-4.01 (m, 5H), 4.19-4.38 (m, 1H), 5.95 (d, J=5.0Hz, 1H), 6.68 (d, J=6.9Hz, 1H), 6.93-6.99 (m, 3H), 7.28-7.44 (m, 8H), 8.41 (d, J=6.9Hz, 1H), 8.73 (d, J=9.7Hz, 1H), 9.15 (br, 1H), 10.80 (br, 1H)
IR (KBr) : 3421, 2929, 1628, 1597, 1535, 1456, 1244 cm^{-1}

Example 38

The following compounds were obtained in a manner similar to Example 37.

(1) 4-N-[[4-N-[2-[N-[(2S)-2-Hydroxy-3-phenoxypropyl]amino]-ethyl]phenyl]amino]-7-quinolinecarboxamide
MS m/z : 457 (MH^+)
^1H NMR (200 MHz, $CDCl_3$) : δ 2.93-3.55 (m, 6H), 3.98-4.01 (m, 2H), 4.17-4.35 (m, 1H), 5.75 (br, 1H), 5.93 (d, J=4.8Hz, 1H), 6.86-7.02 (m, 5H), 7.28-7.40 (m, 5H), 7.67 (br, 1H), 8.07 (dd, J=1.2, 8.8Hz, 1H), 8.32 (br, 1H), 8.44 (d, J=1.2Hz, 1H), 8.53 (d, J=6.0Hz, 1H), 8.64 (d, J=8.8Hz, 1H), 9.91 (br, 1H)
IR (KBr) : 3402, 2929, 1657, 1599, 1412, 1246, 764 cm^{-1}

(2) (2S)-2-[N-[(2S)-2-Hydroxy-3-phenoxypropyl]amino]-3-[4-[(7-methoxy-4-quinolyl)amino]phenyl]propan-1-ol
MS m/z : 474 (MH^+)
IR (KBr) : 3413, 2929, 1624, 1593, 1533, 1514, 1458, 1298, 1244 cm^{-1}

(3) N-Ethyl-4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-N-methyl-7-quinolinecarboxamide
MS m/z : 530 (MH^+)

IR (KBr) : 3881, 1603, 1498, 1423, 1244, 1213 cm^{-1}

(4) 4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-N-propyl-7-quinolinecarboxamide
MS m/z : 530 (MH^+)
IR (KBr) : 3263, 3057, 2960, 2931, 1643, 1597, 1570, 1498, 1431, 1308, 1248, 1213 cm^{-1}

(5) N-[[4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-ethanesulfonamide
MS m/z : 580 (MH^+)
IR (KBr) 3419, 1595, 1554, 1496, 1344, 1246, 1213, 1107 cm^{-1}

(6) N-[[4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-1-propanesulfonamide
MS m/z : 594 (MH^+)
IR (KBr) : 3419, 1595, 1556, 1495, 1346, 1300, 1242, 1211, 1107 cm^{-1}

(7) 4-[[(2S)-2-Hydroxy-3-[N-[(1S)-2-hydroxy-1-[4-[(6-methoxy-4-quinolyl)oxy]benzyl]ethyl]amino]propyl]oxy]-2-(hydroxymethyl)phenol
MS m/z : 521 (MH^+)
IR (KBr) : 3423, 1625, 1579, 1506, 1471, 1369, 1268, 1214 cm^{-1}

(8) (2S)-2-[N-[(2S)-3-(4-9H-Carbazolyloxy)-2-hydroxypropyl]-amino]-3-[4-[(7-methoxy-4-quinolyl)oxy]phenyl]propan-1-ol
MS m/z : 564 (MH^+)
^1H NMR (200 MHz, DMSO-d_6) : δ 2.93-3.64 (m, 8H), 3.94 (s, 3H), 4.25 (br, 2H), 4.41 (br, 1H), 5.36 (br, 1H), 5.89 (br, 1H),

6.43 (d, J=5.2Hz, 1H), 6.72 (d, J=7.8Hz, 1H), 7.08-7.46 (m, 11H), 8.17 (d, J=9.1Hz, 1H), 8.25 (d, J=7.8Hz, 1H), 8.57 (d, J=5.2Hz, 1H), 11.3 (br, 1H)
IR (KBr) : 3404, 1624, 1583, 1506, 1448, 1311, 1228, 1101 cm^{-1}

(9) 4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-N-isopropyl-7-quinolinecarboxamide
MS m/z : 530 (MH^+)
^1H NMR (200 MHz, $CDCl_3$) : δ 1.23 (d, J=6.6Hz, 6H), 2.90-3.66 (m, 8H), 4.00-4.30 (m, 4H), 5.50 (br, 1H), 5.94 (d, J=4.5Hz, 1H), 6.66 (d, J=5.1Hz, 1H), 6.93-7.00 (m, 3H), 7.29-7.36 (m, 4H), 7.47-7.51 (m, 2H), 8.07-8.65 (m, 4H), 8.76 (d, J=5.1Hz, 1H)
IR (KBr) : 3381, 1641, 1597, 1568, 1498, 1427, 1211, 754 cm^{-1}

(10) N-Ethyl-4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolinecarboxamide
MS m/z : 516 (MH^+)

(11) 4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-N-(2-methoxyethyl)-7-quinolinecarboxamide
MS m/z : 546 (MH^+)

(12) 4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-N-(2-methoxyethyl)-N-methyl-7-quinolinecarboxamide
MS m/z : 560 (MH^+)

(13) (2S)-2-[N-[(2S)-2-Hydroxy-3-phenoxypropyl]amino]-3-[4-[[7-(4-morpholinylcarbonyl)-4-quinolyl]oxy]phenyl]propan-1-ol
MS m/z : 558 (MH^+)

(14) (2S)-2-[N-[(2S)-2-Hydroxy-3-phenoxypropyl]amino]-3-[4-[[7-[(4-methyl-1-piperazinyl)carbonyl]-4-quinolyl]oxy]phenyl]propan-1-ol

MS m/z : 571 (MH^+)

(15) (2S)-2-[N-[(2S)-2-Hydroxy-3-phenoxypropyl]amino]-3-[4-[[7-(1-piperazinylcarbonyl)-4-quinolyl]oxy]phenyl]propan-1-ol

MS m/z : 557 (MH^+)

(16) (2S)-2-[N-[(2S)-2-Hydroxy-3-phenoxypropyl]amino]-3-[4-[[7-(1-pyrrolidinylcarbonyl)-4-quinolyl]oxy]phenyl]propan-1-ol

MS m/z : 542 (MH^+)

(17) Ethyl N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]-carbonyl]glycinate

MS m/z : 574 (MH^+)

^1H NMR (200 MHz, DMSO-d_6) : δ 1.23 (t, J=7.1Hz, 3H), 2.77-3.53 (m, 8H), 3.86-3.96 (m, 3H), 4.08 (d, J=5.8Hz, 2H), 4.15 (q, J=7.1Hz, 2H), 4.76 (br, 1H), 5.12 (br, 1H), 6.64 (d, J=5.2Hz, 1H), 6.87-6.95 (m, 3H), 7.19-7.41 (m, 6H), 8.09 (dd, J=1.6, 8.7Hz, 1H), 8.40 (d, J=8.7Hz, 1H), 8.57 (d, J=1.3Hz, 1H), 8.74 (d, J=5.2Hz, 1H), 9.32 (t, J=5.8Hz, 1H)

(18) N-(2-Hydroxyethyl)-4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolinecarboxamide

MS m/z : 532 (MH^+)

(19) Ethyl N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate

MS m/z : 588 (MH^+)

(20) Ethyl N-[[4-[4-[2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]ethyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate
MS m/z : 558 (MH^+)

(21) Ethyl 4-[[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-amino]butanoate
MS m/z : 602 (MH^+)

(22) Ethyl N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-N-methyl-beta-alaninate
MS m/z : 602 (MH^+)

(23) Ethyl [[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]oxy]acetate
MS m/z : 547 (MH^+)

(24) Ethyl [[4-[4-[2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]ethyl]phenoxy]-7-quinolyl]oxy]acetate dihydrochloride
MS m/z : 517 (MH^+)

(25) 4-[4-[(2S)-3-Hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-N,N-dimethyl-8-quinolinecarboxamide
(+)ESI-MS m/z : 516 $(M+H)^+$

(26) 4-[4-[(2S)-3-Hydroxy-2-[N-((2S)-2-hydroxy-3-(4-hydroxyphenoxy)propyl)amino]propyl]phenoxy]-N,N-dimethyl-8-quinolinecarboxamide
(+)ESI-MS m/z : 532 $(M+H)^+$

(27) Ethyl [[[4-[4-[(2S)-3-hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-8-quinolyl]carbonyl]-amino]acetate
(+)APCI-MS m/z : 574 $(M+H)^+$

(28) Ethyl 3-[[[4-[4-[(2S)-3-hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-8-quinolyl]carbonyl]-amino]propanoate
(+)ESI-MS m/z : 588 $(M+H)^+$

(29) Ethyl 4-[4-[(2S)-3-hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-7-quinolinecarbamate
(+)ESI-MS m/z : 532 $(M+H)^+$

(30) N-[[4-[4-[(2S)-2-[N-[(2S)-3-(4-9H-Carbazolyloxy)-2-hydroxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]methanesulfonamide
(-)ESI-MS m/z : 652, 654 $(M-H)^-$

(31) (S)-4-[4-[2-[N-(2-Hydroxy-3-phenoxypropyl)amino]ethyl]-phenoxy]-N-propyl-7-quinolinecarboxamide
(+)ESI-MS m/z : 500 $(M+H)^+$

(32) (S)-4-[4-[2-[N-(2-Hydroxy-3-phenoxypropyl)amino]ethyl]-phenoxy]-N,N-dimethyl-7-quinolinecarboxamide
(+)ESI-MS m/z : 486 $(M+H)^+$

(33) (S)-4-[4-[2-[N-(2-Hydroxy-3-phenoxypropyl)amino]ethyl]-phenoxy]-N-(2,2,2-trifluoroethyl)-7-quinolinecarboxamide
(+)ESI-MS m/z : 540 $(M+H)^+$

(34) (S)-N-[[4-[4-(2-[N-(2-Hydroxy-3-phenoxypropyl)amino]-

ethyl)phenoxy]-7-quinolyl]carbonyl]-1-propanesulfonamide
(-)ESI-MS m/z : 562 $(M-H)^-$

(35) (S)-1-[N-[2-[4-[(7-Methoxy-4-quinolyl)oxy]phenyl]-ethyl]amino]-3-phenoxypropan-2-ol
(+)ESI-MS m/z : 445 $(M+H)^+$

(36) 4-[4-[(2S)-3-Hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-N,N-dimethyl-6-quinolinecarboxamide
(+)APCI-MS m/z : 516 $(M+H)^+$

(37) (2S)-2-[N-[(2S)-3-(4-9H-Carbazolyloxy)-2-hydroxypropyl]-amino]-3-[4-(4-quinazolinyloxy)phenyl]propan-1-ol
(+)APCI-MS m/z : 535 $(M+H)^+$

(38) N-[[4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-1-butanesulfonamide
MS (negative) m/z : 606 $(M-H^+)$

(39) N-[[4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-1-pentanesulfonamide
MS (negative) m/z : 620 $(M-H^+)$

(40) N-[[4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-benzenesulfonamide
MS (negative) m/z : 626 $(M-H^+)$

(41) N-[[4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-2-

propanesulfonamide
MS (negative) m/z : 592 ($M-H^+$)

(42) 1,1,1-Trifluoro-N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]-carbonyl]methanesulfonamide
MS (negative) m/z : 618 ($M-H^+$)

Example 39

To a solution of 4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenol (300 mg) in dimethyl sulfoxide (6.0 ml) was added potassium tert-butoxide (90.9 mg) and the mixture was stirred at room temperature for 1 hour. To the mixture was added 4-chloro-N-ethyl-N-methyl-7-quinolinecarboxamide (238 mg) and the whole was stirred at 100°C for 20 hours. After cooling to room temperature, the mixture was diluted with ethyl acetate (30 ml), washed with water (30 ml×2) and brine (30 ml×1), and dried over magnesium sulfate. Filtration followed by evaporation gave a pale-yellow foam. The crude product was chromatographed on 25 g of silica gel (ethyl acetate) to give 4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-N-ethyl-N-methyl-7-quinolinecarboxamide (146 mg) as a white foam.
MS m/z : 620 (MH^+)

Example 40

The following compounds were obtained in a manner similar to Example 39.

(1) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]-3-hydroxypropyl]phenoxy]-N-propyl-7-quinolinecarboxamide

MS m/z 620 (MH^+)

(2) 4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-N-propyl-7-quinolinecarboxamide
MS m/z : 624 (MH^+)

(3) N-[[4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]ethanesulfonamide
MS m/z : 670 (MH^+)

(4) N-[[4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]-1-propanesulfonamide
MS m/z : 684 (MH^+)

(5) N-[[4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]ethanesulfonamide
MS m/z : 674 (MH^+)

(6) N-[[4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]-1-propanesulfonamide
MS m/z : 688 (MH^+)

(7) (2S)-2-[N-Benzyl-N-[(2S)-3-(4-9H-carbazolyloxy)-2-hydroxypropyl]amino]-3-[4-[(7-methoxy-4-quinolyl)oxy]phenyl]-propan-1-ol
MS m/z : 654 (MH^+)

(8) (2S)-2-[N-[(2S)-2-Hydroxy-3-(4-1H-

indolyloxy)propyl]amino]-3-[4-[(7-methoxy-4-quinolyl)oxy]-phenyl]propan-1-ol

MS m/z : 514 (MH^+)

IR (KBr) : 3401, 2925, 1621, 1581, 1506, 1444, 1429, 1313, 1228 cm^{-1}

(9) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarboxylic acid

MS m/z : 579 (MH^+)

(10) 4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarboxylic acid

MS m/z : 583 and 585 (MH^+)

(11) N-[[4-[4-[2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]-7-quinolyl]carbonyl]-methanesulfonamide

MS (negative) m/z : 628 and 630 ($M-H^+$)

(12) 4-[4-[2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]-7-quinolinecarboxylic acid

MS m/z : 553 (MH^+)

(13) 4-[4-[2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]ethyl]phenoxy]-N,N-dimethyl-8-quinolinecarboxamide

MS m/z : 576 (MH^+)

(14) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-N-(2-hydroxyethyl)-8-quinolinecarboxamide

MS m/z : 622 (MH^+)

(15) 4-[4-[2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]-N-(2-hydroxyethyl)-8-quinolinecarboxamide
MS m/z : 592 (MH^+)

(16) tert-Butyl [[4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]oxy]-acetate
MS m/z : 665 (MH^+)

(17) tert-Butyl [[4-[4-[2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]-7-quinolyl]oxy]acetate
MS m/z : 635 (MH^+)

(18) tert-Butyl [[4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]oxy]acetate
MS m/z : 669 and 671 (MH^+)

(19) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-8-quinolinecarboxamide
(+)APCI-MS m/z : 606 $(M+H)^+$

(20) 4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-8-quinolinecarboxamide
(+)ESI-MS m/z : 610, 612 $(M+H)^+$

(21) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-3-[4-(benzyloxy)phenoxy]-2-hydroxypropyl]amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-8-quinolinecarboxamide
(+)ESI-MS m/z : 712 $(M+H)^+$

(22) 4-[4-[(2S)-2-[N-Benzyl-N-((2S)-2-hydroxy-3-phenoxypropyl)amino]-3-hydroxypropyl]phenoxy]-N-ethyl-8-quinolinecarboxamide
(+)APCI-MS m/z : 606 $(M+H)^+$

(23) 4-[4-[(2S)-2-[N-Benzyl-N-((2S)-2-hydroxy-3-phenoxypropyl)amino]-3-hydroxypropyl]phenoxy]-N-ethyl-N-methyl-8-quinolinecarboxamide
(+)APCI-MS m/z : 620 $(M+H)^+$

(24) 4-[4-[(2S)-2-[N-Benzyl-N-((2S)-2-hydroxy-3-phenoxypropyl)amino]-3-hydroxypropyl]phenoxy]-N-(2,2,2-trifluoroethyl)-8-quinolinecarboxamide
(+)ESI-MS m/z : 660 $(M+H)^+$

(25) tert-Butyl [[[4-[4-[(2S)-2-[N-benzyl-N-((2S)-2-hydroxy-3-phenoxypropyl)amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]-carbonyl]amino]acetate
(+)ESI-MS m/z : 692 $(M+H)^+$

(26) tert-Butyl [[[4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]carbonyl]amino]acetate
(+)ESI-MS m/z : 696, 698 $(M+H)^+$

(27) tert-Butyl 3-[[[4-[4-[(2S)-2-[N-benzyl-N-((2S)-2-hydroxy-3-phenoxypropyl)amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]-carbonyl]amino]propanoate
(+)ESI-MS : 706 $(M+H)^+$

(28) tert-Butyl 3-[[[4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-

8-quinolyl]carbonyl]amino]propanoate
(+)ESI-MS m/z : 710, 712 $(M+H)^+$

(29) 4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-N-(2-hydroxyethyl)-8-quinolinecarboxamide
(+)ESI-MS m/z : 626, 628 $(M+H)^+$

(30) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-(4-1H-indolyloxy)propyl]amino]-3-hydroxypropyl]phenoxy]-N-(2-hydroxyethyl)-8-quinolinecarboxamide
(+)APCI-MS m/z : 661 $(M+H)^+$

(31) (S)-4-[4-[2-[N-Benzyl-N-(2-hydroxy-3-phenoxypropyl)-amino]ethyl]phenoxy]-N-ethyl-8-quinolinecarboxamide
(+)APCI-MS m/z : 576 $(M+H)^+$

(32) (S)-4-[4-[2-[N-Benzyl-N-(2-hydroxy-3-phenoxypropyl)-amino]ethyl]phenoxy]-N-(2,2,2-trifluoroethyl)-8-quinolinecarboxamide
(+)APCI-MS m/z : 630 $(M+H)^+$

(33) (S)-4-[4-[2-[N-Benzyl-N-(2-hydroxy-3-phenoxypropyl)-amino]ethyl]phenoxy]-N-ethyl-N-methyl-8-quinolinecarboxamide
(+)APCI-MS m/z : 590 $(M+H)^+$

(34) (2S)-2-[N-Benzyl-N-((2S)-2-hydroxy-3-phenoxypropyl)-amino]-3-[4-[(7-nitro-4-quinolyl)oxy]phenyl]propan-1-ol
(+)APCI-MS m/z : 580 $(M+H)^+$

(35) (2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-[4-[(7-nitro-4-quinolyl)oxy]phenyl]-propan-1-ol

(+)APCI-MS m/z : 584, 586 $(M+H)^+$

(36) 4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-7-quinolinecarboxamide
(+)ESI-MS m/z : 520, 522 $(M+H)^+$

(37) 4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-N-methyl-7-quinolinecarboxamide
(+)ESI-MS m/z : 506, 508 $(M+H)^+$

(38) N-[[4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-3-(4-9H-carbazolyloxy)-2-hydroxypropyl]amino]-3-hydroxypropyl]-phenoxy]-7-quinolyl]carbonyl]methanesulfonamide
(-)ESI-MS m/z : 743 $(M-H)^-$

(39) N-[[4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-(4-1H-indolyloxy)propyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]carbonyl]methanesulfonamide
(-)ESI-MS m/z : 693 $(M-H)^-$

(40) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-3-(4-fluorophenoxy)-2-hydroxypropyl]amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-7-quinolinecarboxamide
(+)APCI-MS m/z : 624 $(M+H)^+$

(41) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-3-(4-fluorophenoxy)-2-hydroxypropyl]amino]-3-hydroxypropyl]phenoxy]-N-methyl-7-quinolinecarboxamide
(+)ESI m/z : 610 $(M+H)^+$

(42) (S)-4-[4-[2-[N-Benzyl-N-[(2S)-2-hydroxy-3-

(phenoxy)propyl]amino]ethyl]phenoxy]-7-quinolinecarboxylic acid
(+)ESI-MS m/z : 549 $(M+H)^+$

(43) (S)-1-[N-Benzyl-N-[2-[4-[(7-methoxy-4-quinolyl)oxy]-phenyl]ethyl]amino]-3-phenoxypropan-2-ol
(+)APCI-MS m/z : 535 $(M+H)^+$

(44) 4-[4-[(2S)-2-[N-Benzyl-N-((2S)-2-hydroxy-3-phenoxypropyl)amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-6-quinolinecarboxamide
(+)APCI-MS m/z : 606 $(M+H)^+$

(45) 4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-6-quinolinecarboxamide
(+)APCI-MS m/z : 610, 612 $(M+H)^+$

(46) 4-[4-[(2S)-3-Hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-N,N-dimethyl-2-quinolinecarboxamide
(+)APCI-MS m/z : 516 $(M+H)^+$

(47) 4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-2-quinolinecarboxamide
(+)ESI-MS m/z : 520, 522 $(M+H)^+$

(48) 4-[4-[(2S)-3-Hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-N,N-dimethyl-3-quinolinecarboxamide
(+)ESI-MS m/z : 516 $(M+H)^+$

(49) 4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-3-quinolinecarboxamide
(+)APCI-MS m/z : 610, 612 $(M+H)^+$

(50) (2S)-2-[N-Benzyl-N-[(2S)-3-(4-9H-carbazolyloxy)-2-hydroxypropyl]amino]-3-[4-(4-quinazolinyloxy)phenyl]propan-1-ol
(+)APCI-MS m/z : 625 $(M+H)^+$

(51) (2S)-2-[N-[(2S)-2-Hydroxy-3-(4-1H-indolyloxy)propyl]-amino]-3-[4-(4-quinazolinyloxy)phenyl]propan-1-ol
(+)APCI-MS m/z : 485 $(M+H)^+$

(52) N-[[4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]-1-butanesulfonamide
MS (negative) m/z : 696 $(M-H^+)$

(53) N-[[4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]-1-pentanesulfonamide
MS (negative) m/z : 710 $(M-H^+)$

(54) N-[[4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]benzenesulfonamide
MS (negative) m/z : 716 $(M-H^+)$

(55) N-[[4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]-2-propanesulfonamide
MS (negative) m/z : 682 $(M-H^+)$

(56) N-[[4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]-1,1,1-trifluoromethanesulfonamide
MS (negative) m/z : 708 ($M-H^+$)

Example 41

The following compounds were obtained in a manner similar to Preparation 29.

(1) 5-[[(2S)-3-[N-Benzyl-N-[(1S)-2-hydroxy-1-[4-[(6-methoxy-4-quinolyl)oxy]benzyl]ethyl]amino]-2-hydroxypropyl]oxy]-2-(benzyloxy)benzaldehyde
MS m/z : 699 (MH^+)

(2) Ethyl N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-(1H-indol-4-yloxy)propyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate
MS m/z : 627 (MH^+)

Example 42

To a solution of 5-[[(2S)-3-[N-benzyl-N-[(1S)-2-hydroxy-1-[4-[(6-methoxy-4-quinolyl)oxy]benzyl]ethyl]amino]-2-hydroxypropyl]oxy]-2-(benzyloxy)benzaldehyde (101 mg) in a mixed solvent of tetrahydrofuran (1.0 ml) and ethanol (1.0 ml) was added sodium borohydride (10.9 mg) at room temperature. After stirring for 2 hours, the reaction mixture was diluted with ethyl acetate (20 ml) and washed with water (20 ml×2), brine (20 ml×1), dried over magnesium sulfate, and evaporated to give a white foam (103 mg). The crude product was purified by recycling preparative high pressure liquid chromatography equipped with a gel permeation chromatography column (chloroform) to give (2S)-2-[N-benzyl-N-[(2S)-3-[4-

(benzyloxy)-3-(hydroxymethyl)phenoxy]-2-hydroxypropyl]amino]-3-[4-[(6-methoxy-4-quinolyl)oxy]phenyl]propan-1-ol (51.3 mg) as a pale-yellow foam.

MS m/z : 701 (MH^+)

Example 43

To a solution of 4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-N-propyl-7-quinolinecarboxamide (182 mg) in a mixed solvent of methanol (3.0 ml) and chlorobenzene (3.0 ml) was added 10% palladium on activated carbon (50% wet, 90 mg) and the mixture was hydrogenated at 1 atm for 2 hours. The mixture was filtered, washed with methanol, and concentrated in vacuo to give 4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-N-propyl-7-quinolinecarboxamide dihydrochloride (177 mg) as a pale-brown solid.

MS m/z : 534 (MH^+)

IR (KBr) : 3357, 2964, 2933, 1645, 1593, 1544, 1493, 1433, 1302, 1200 cm^{-1}

Example 44

The following compounds were obtained in a manner similar to Example 43.

(1) N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]carbonyl]ethanesulfonamide dihydrochloride

MS m/z :584 (MH^+)

IR (KBr) : 3381, 1695, 1593, 1496, 1429, 1304, 1198, 1153 cm^{-1}

(2) N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-

quinolyl]carbonyl]-1-propanesulfonamide dihydrochloride
MS m/z : 598 (MH^+)
IR (KBr) : 3390, 1695, 1643, 1593, 1496, 1429, 1304, 1198, 1151 cm^{-1}

(3) 4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenoxy]-N-ethyl-7-quinolinecarboxamide dihydrochloride
MS m/z : 520 and 522 (MH^+)

(4) 4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenoxy]-N-(2-methoxyethyl)-7-quinolinecarboxamide dihydrochloride
MS m/z : 550 and 552 (MH^+)

(5) 4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenoxy]-N-(2-methoxyethyl)-N-methyl-7-quinolinecarboxamide dihydrochloride
MS m/z : 564 and 566 (MH^+)

(6) N-[[4-[4-[2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]ethyl]phenoxy]-7-quinolyl]carbonyl]methanesulfonamide dihydrochloride
MS m/z : 540 and 542 (MH^+)
^1H NMR (200 MHz, DMSO-d_6): δ 3.46-4.84 (m, 10H), 5.87 (d, J=7.8Hz, 1H), 7.64 (d, J=5.4Hz, 1H), 8.15-8.31 (m, 9H), 8.72 (br, 1H), 8.99 (d, J=8.5Hz, 1H), 9.32 (d, J=8.5Hz, 1H), 9.54 (s, 1H), 9.73 (d, J=5.4Hz, 1H), 9.76 (br, 1H), 10.1 (br, 1H)

(7) 4-[4-[2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]phenoxy]-N-ethyl-7-quinolinecarboxamide dihydrochloride
MS m/z : 490 and 492 (MH^+)
^1H NMR (200 MHz, DMSO-d_6): δ 1.20 (t, J=7.1Hz, 3H), 3.17-3.42

(m, 9H), 5.10 (d, J=8.3Hz, 1H), 6.98 (d, J=5.9Hz, 1H), 7.41-7.55 (m, 9H), 8.31 (d, J=8.7Hz, 1H), 8.72 (s, 1H), 9.05 (d, J=9.5Hz, 1H), 9.11-9.13 (m, 2H), 9.52 (br, 1H)

(8) 4-[4-[2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]amino]-ethyl]phenoxy]-N-propyl-7-quinolinecarboxamide dihydrochloride
MS m/z 504 and 506 (MH^+)
^1H NMR (200 MHz, DMSO-d_6): δ 0.94 (t, J=7.3Hz, 3H), 1.56-1.67 (m, 2H), 3.18-3.33 (m, 9H), 5.11 (d, J=8.6Hz, 1H), 6.98 (d, J=6.1Hz, 1H), 7.41-7.55 (m, 9H), 8.31 (d, J=8.8Hz, 1H), 8.60 (d, J=8.8Hz, 1H), 8.73 (s, 1H), 9.05 (d, J=6.1Hz, 1H), 9.09-9.12 (m, 2H), 9.55 (br, 1H)

(9) 4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-8-quinolinecarboxamide dihydrochloride
(+)ESI-MS m/z : 520, 522 $(M-2HCl+H)^+$

(10) 4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenoxy]-N-(2-hydroxyethyl)-8-quinolinecarboxamide dihydrochloride
(+)APCI-MS m/z : 536, 538 $(M-2HCl+H)^+$

(11) Ethyl 4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarbamate dihydrochloride
(+)ESI-MS m/z : 536, 538 $(M-2HCl+H)^+$

(12) 4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-6-quinolinecarboxamide dihydrochloride
(+)APCI-MS m/z : 520, 522 $(M+H)^+$

(13) 4-[4-[(2S)-2-[N-[(2R)-2-(3-Chlorophenyl)-2-hydroxyethyl]-amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-3-quinolinecarboxamide
(+)ESI-MS m/z : 520, 522 $(M+H)^+$

(14) Ethyl [[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]-carbonyl]amino]acetate
(+)APCI-MS m/z : 578, 580 $(M+H)^+$

(15) Ethyl 3-[N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]-carbonyl]amino]propanoate
(+)ESI-MS m/z : 592, 594 $(M+H)^+$

Example 45

To a solution of 4-[4-[2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]-N,N-dimethyl-8-quinolinecarboxamide (712 mg) in methanol (20 mL) was added 10% palladium on activated carbon (50% wet, 350 mg) and the mixture was hydrogenated at 1 atm for 1.5 hours. The catalyst was filtered off and washed with methanol. To the filtrate was added 4N hydrogen chloride in dioxane (2.0 mL) and the solvent was concentrated in vacuo to give 4-[4-[2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]-N,N-dimethyl-8-quinolinecarboxamide dihydrochloride (710 mg) as a white solid.
MS m/z : 486 (MH^+)
IR (KBr) : 3421, 2933, 1630, 1585, 1475, 1408, 1296, 1246, 1201, 760 cm^{-1}

Example 46

The following compounds were obtained in a manner similar to Example 45.

(1) N-(2-Hydroxyethyl)-4-[4-[2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]-8-quinolinecarboxamide dihydrochloride
MS m/z : 502 (MH^+)
IR (KBr) 3383, 3059, 2939, 1631, 1597, 1583, 1419, 1296, 1242, 1200 cm^{-1}

(2) N-(2-Hydroxyethyl)-4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-8-quinolinecarboxamide dihydrochloride
MS m/z : 532 (MH^+)
IR (KBr) : 3357, 3060, 2933, 1631, 1597, 1583, 1419, 1296, 1242, 1201, 1063, 758 cm^{-1}

(3) N-Ethyl-4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-8-quinolinecarboxamide dihydrochloride
(+)APCI-MS m/z : 516 $(M+H)^+$

(4) N-Ethyl-4-[4-[(2S)-3-hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-N-methyl-8-quinolinecarboxamide dihydrochloride
(+)APCI-MS m/z : 530 $(M-HCl+H)^+$

(5) 4-[4-[(2S)-3-Hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-N-(2,2,2-trifluoroethyl)-8-quinolinecarboxamide dihydrochloride
(+)APCI-MS m/z : 570 $(M-2HCl+H)^+$

(6) N-(2-Hydroxyethyl)-4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-(1H-indol-4-yloxy)propyl]amino]propyl]phenoxy]-8-quinolinecarboxamide dihydrochloride

(+)ESI-MS m/z : 571 $(M+H)^+$

(7) (S)-N-Ethyl-4-[4-[2-[N-(2-hydroxy-3-phenoxypropyl)amino]-ethyl]phenoxy]-8-quinolinecarboxamide dihydrochloride
(+)APCI-MS m/z : 486 $(M-2HCl+H)^+$

(8) (S)-4-[4-[2-[N-(2-Hydroxy-3-phenoxypropyl)amino]ethyl]-phenoxy]-N-(2,2,2-trifluoroethyl)-8-quinolinecarboxamide dihydrochloride
(+)APCI-MS m/z : 540 $(M-2HCl+H)^+$

(9) (S)-N-Ethyl-4-[4-[2-[N-(2-hydroxy-3-phenoxypropyl)amino]-ethyl]phenoxy]-N-methyl-8-quinolinecarboxamide dihydrochloride
(+)APCI-MS m/z : 500 $(M-2HCl+H)^+$

(10) N-[[4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-(4-1H-indolyloxy)propyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-methanesulfonamide dihydrochloride
(-)ESI-MS m/z : 603 $(M-2HCl-H)^-$

(11) 4-[4-[(2S)-2-[N-[(2S)-3-(4-Fluorophenoxy)-2-hydroxypropyl]amino]-3-hydroxypropyl]phenoxy]-N,N-dimethyl-7-quinolinecarboxamide
(+)APCI-MS m/z : 534 $(M+H)^+$

(12) 4-[4-[(2S)-2-[N-[(2S)-3-(4-Fluorophenoxy)-2-hydroxypropyl]amino]-3-hydroxypropyl]phenoxy]-N-methyl-7-quinolinecarboxamide
(+)APCI-MS m/z : 520 $(M+H)^+$

Example 47

To a solution of ethyl N-[[4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-

hydroxypropyl]phenoxy]-7-quinolyl]carbonyl]glycinate (168 mg) in a mixed solvent of methanol (2.5 ml) and chlorobenzene (2.5 ml) was added 10% palladium on activated carbon (50% wet, 168 mg) and the mixture was hydrogenated at 1 atm for 90 minutes. The catalyst was removed by filtration and washed with methanol. The filtrate was concentrated in vacuo to give an orange solid (159 mg). The solid was chromatographed on 15 g of silica gel (NH-DM1020, Fuji Silysia Chemical Ltd., chloroform : methanol = 50 : 1) to give ethyl N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]carbonyl]glycinate (94.2 mg) as a white solid.

MS m/z : 578 and 580 (MH^+)

Example 48

The following compounds were obtained in a manner similar to Example 47.

(1) Ethyl N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]-beta-alaninate

MS m/z : 592 and 594 (MH^+)

(2) Ethyl [[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-oxy]acetate

MS m/z : 551 and 553 (MH^+)

Example 49

To a suspension of 4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarboxylic acid (117 mg) in dichloromethane (2.3 ml) were added successively 1-hydroxybenzotriazole hydrate (32.8

mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (46.5 mg) at 0°C. After stirring at the same temperature for 5 minutes, isopropylamine (20.7 μl) was added, and the resulting solution was warmed to room temperature. After 75 minutes, another portion of isopropylamine (20.7 μl) was added. The stirring was continued at room temperature for 20 hours. The reaction mixture was diluted with ethyl acetate (20 ml) and washed with water (20 ml×3) and brine (20 ml×1), and dried over magnesium sulfate. Filtration followed by evaporation gave a pale-yellow foam (132 mg). The crude product was purified by recycling preparative high pressure liquid chromatography equipped with a gel permeation chromatography column (chloroform) to give 4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-N-isopropyl-7-quinolinecarboxamide (91.0 mg) as a white foam.

MS m/z : 620 (MH^+)

Example 50

The following compounds were obtained in a manner similar to Example 49.

(1) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]-3-hydroxypropyl]phenoxy]-N-ethyl-7-quinolinecarboxamide

MS m/z : 606 (MH^+)

(2) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]-3-hydroxypropyl]phenoxy]-N-(2-methoxyethyl)-7-quinolinecarboxamide

MS m/z : 636 (MH^+)

(3) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]-amino]-3-hydroxypropyl]phenoxy]-N-(2-methoxyethyl)-N-methyl-7-

quinolinecarboxamide
MS m/z : 650 (MH^+)

(4) (2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-[[7-(4-morpholinylcarbonyl)-4-quinolyl]oxy]phenyl]propan-1-ol
MS m/z : 648 (MH^+)

(5) (2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-[[7-[(4-methyl-1-piperazinyl)carbonyl]-4-quinolyl]-oxy]phenyl]propan-1-ol
MS m/z : 661 (MH^+)

(6) (2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-[[7-[(4-benzyl-1-piperazinyl)carbonyl]-4-quinolyl]oxy]phenyl]propan-1-ol
MS m/z : 737 (MH^+)

(7) (2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-[4-[[7-(1-pyrrolidinylcarbonyl)-4-quinolyl]oxy]phenyl]-propan-1-ol
MS m/z : 632 (MH^+)

(8) 4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-N-ethyl-7-quinolinecarboxamide
MS m/z : 610 and 612 (MH^+)

(9) 4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-N-(2-methoxyethyl)-7-quinolinecarboxamide
MS m/z : 640 and 642 (MH^+)

(10) 4-[4-[(2S)-2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-N-(2-methoxyethyl)-N-methyl-7-quinolinecarboxamide

MS m/z : 654 and 656 (MH^+)

(11) Ethyl N-[[4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]glycinate

MS m/z : 664 (MH^+)

(12) 4-[4-[2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]-N-ethyl-7-quinolinecarboxamide

MS m/z : 580 and 582 (MH^+)

(13) 4-[4-[2-[N-Benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]ethyl]phenoxy]-N-propyl-7-quinolinecarboxamide

MS m/z : 594 and 596 (MH^+)

(14) 4-[4-[(2S)-2-[N-Benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-N-(2-hydroxyethyl)-7-quinolinecarboxamide

MS m/z : 622 (MH^+)

(15) Ethyl N-[[4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]-beta-alaninate

MS m/z : 678 (MH^+)

(16) Ethyl N-[[4-[4-[2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate

MS m/z : 648 (MH^+)

(17) Ethyl N-[[4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]carbonyl]glycinate
MS m/z : 668 and 670 (MH^+)

(18) Ethyl N-[[4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate
MS m/z : 682 and 684 (MH^+)

(19) Ethyl 4-[[[4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]amino]butanoate
MS m/z : 692 (MH^+)

(20) Ethyl N-[[4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]-N-methyl-beta-alaninate
MS m/z : 692 (MH^+), 714 ($M+Na^+$)

Example 51

Under nitrogen at 5°C, a solution of (S)-4-[4-[2-[N-benzyl-N-(2-hydroxy-3-phenoxypropyl)amino]ethyl]phenoxy]-7-quinolinecarboxylic acid (300 mg) in N,N-dimethylformamide (6 ml) were added n-propylamine (0.054 ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (130 mg) and 1-hydroxybenzotriazole (89 mg), and the mixture was stirred at room temperature for 12 hours. The resulting mixture was poured into water and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over anhydrous

magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform : methanol = 200 : 1 to 50 : 1) to give (S)-4-[4-[2-[N-benzyl-N-(2-hydroxy-3-phenoxypropyl)amino]ethyl]-phenoxy]-N-propyl-7-quinolinecarboxamide (270 mg).
(+)ESI-MS m/z : 590 $(M+H)^+$

Example 52

The following compounds were obtained in a manner similar to Example 51.

(1) (S)-4-[4-[2-[N-(2-Hydroxy-3-phenoxypropyl)amino]-ethyl]phenoxy]-N,N-dimethyl-7-quinolinecarboxamide
(+)APCI-MS m/z : 576 $(M+H)^+$

(2) (S)-4-[4-[2-[N-Benzyl-N-(2-hydroxy-3-phenoxypropyl)-amino]ethyl]phenoxy]-N-(2,2,2-trifluoroethyl)-7-quinolinecarboxamide
(+)ESI-MS m/z : 630 $(M+H)^+$

Example 53

Under nitrogen at room temperature, to a solution of (S)-N-[[4-[4-[2-[N-benzyl-N-[2-[[(tert-butyl)dimethylsilyl]oxy]-3-phenoxypropyl]amino]ethyl]phenoxy]-7-quinolyl]carbonyl]-1-propanesulfonamide (280 mg) in tetrahydrofuran (5 ml) was added tetrabutylammonium fluoride (1M in tetrahydrofuran, 1.1 ml), and the mixture was stirred at the same temperature for 24 hours. The resulting mixture was poured into buffer solution (pH 4) and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with buffer solution (pH 4), dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel

(chloroform : methanol = 50 : 1 to 20 : 1) to give (S)-N-[[4-[4-[2-[N-benzyl-N-(2-hydroxy-3-phenoxypropyl)amino]ethyl]-phenoxy]-7-quinolyl]carbonyl]-1-propanesulfonamide (200 mg).
(-)ESI-MS m/z : 652 $(M-H)^-$

Example 54

Ethyl N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate (12.0 mg) was dissolved in 4N hydrogen chloride in ethanol (100 µl). The solvent was removed by evaporation to give N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate dihydrochloride (13.8 mg) as a white solid.
MS m/z : 588 (MH^+)

Example 55

The following compounds were obtained in a manner similar to Example 54.

(1) N-[[4-[4-[2-[N-[(2S)-2-Hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate dihydrochloride
MS m/z : 558 (MH^+)

(2) Ethyl N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]glycinate dihydrochloride
MS m/z : 578 (MH^+)

(3) Ethyl N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]-beta-alaninate dihydrochloride
MS m/z : 592 (MH^+)

(4) Ethyl 4-[[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-amino]butanoate dihydrochloride

MS m/z : 602 (MH^+)

(5) Ethyl N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-N-methyl-beta-alaninate dihydrochloride

MS m/z : 602 (MH^+)

(6) Ethyl [[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]oxy]acetate dihydrochloride

MS m/z : 547 (MH^+)

(7) Ethyl [[4-[4-[2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]-7-quinolyl]oxy]acetate dihydrochloride

MS m/z : 607 (MH^+)

(8) Ethyl [[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]oxy]-acetate dihydrochloride

MS m/z : 551 and 553 (MH^+)

(9) Ethyl N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-(1H-indol-4-yloxy)propyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate dihydrochloride

MS m/z : 627 (MH^+)

(10) Ethyl [N-[[4-[4-[(2S)-3-hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-8-quinolyl]carbonyl]-

amino]acetate dihydrochloride
(+)ESI-MS m/z : 574 $(M-2HCl+H)^+$

(11) Ethyl N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]-carbonyl]glycinate dihydrochloride
(+)ESI-MS m/z : 578, 580 $(M-2HCl+H)^+$

(12) Ethyl N-[[4-[4-[(2S)-3-hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-8-quinolyl]carbonyl]-beta-alaninate dihydrochloride
(+)ESI-MS m/z : 588 $(M-2HCl+H)^+$

(13) Ethyl N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]-carbonyl]-beta-alaninate dihydrochloride
(+)ESI-MS m/z : 592, 594 $(M-2HCl+H)^+$

Example 56

To a suspension of N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]-carbonyl]glycinate (62.9 mg) in ethanol (2.0 ml) was added 1N sodium hydroxide solution (110 ml) at room temperature and the mixture was stirred for 24 hours. The solvent was removed by evaporation to give sodium N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]glycinate (60.6 mg) as a white crystalline solid.
MS (negative) m/z : 544 $(M-Na^+)$
^1H NMR (200 MHz, DMSO-d_6): δ 1.90 (br, 1H), 2.58-2.84 (m, 5H), 3.33-3.43 (m, 2H), 3.55 (d, J=4.6Hz, 2H), 3.82-3.94 (m, 3H), 4.63 (br, 1H), 4.96 (br, 1H), 6.60 (d, J=5.2Hz, 1H), 6.90-6.94 (m, 3H), 7.17-7.39 (m, 6H), 8.04 (d, J=8.7Hz, 1H), 8.16 (br,

1H), 8.37 (d, J=8.7Hz, 1H), 8.44 (s, 1H), 8.72 (d, J=5.2Hz, 1H).

IR (KBr) : 3423, 2925, 1641, 1597, 1502, 1427, 1390, 1248, 1217 cm^{-1}

Example 57

The following compounds were obtained in a manner similar to Example 56.

(1) Sodium N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate

MS m/z : 582 (MH^+)

^1H NMR ($CDCl_3$, DMSO-d_6): δ 1.89 (br, 1H), 2.17 (t, J=6.9Hz, 2H), 2.60-2.78 (m, 5H), 3.42-3.48 (m, 4H), 3.83-3.94 (m, 4H), 4.65 (br, 1H), 4.99 (br, 1H), 6.60 (d, J=5.2Hz, 1H), 6.86-6.94 (m, 3H), 7.16-7.38 (m, 6H), 8.03 (dd, J=1.6, 8.7Hz, 1H), 8.36 (d, J=8.7Hz, 1H), 8.71 (d, J=5.2Hz, 1H), 9.44 (t, J=5.0Hz, 1H)

(2) Sodium N-[[4-[4-[2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate

MS m/z : 552 (MH^+)

(3) Sodium N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]glycinate

MS (negative) m/z : 548 ($M-Na^+$)

(4) Sodium N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]-carbonyl]-beta-alaninate

MS (negative) m/z : 562 ($M-Na^+$)

(5) Sodium 4-[N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-amino]butanoate
MS m/z : 596 (MH^+)

(6) Sodium N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-N-methyl-beta-alaninate
MS m/z : 596 (MH^+)

(7) Sodium [[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]oxy]acetate
MS m/z : 541 (MH^+)

(8) Sodium [[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]oxy]-acetate
MS (negative) m/z : 521 ($M-Na^+$)

(9) Sodium N-[[4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-(4-1H-indolyloxy)propyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-beta-alaninate
MS m/z : 621 (MH^+)

(10) Sodium N-[[4-[4-[(2S)-3-hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-8-quinolyl]carbonyl]-glycinate
(+)ESI-MS m/z : 568 $(M+H)^+$

(11) Sodium N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]-carbonyl]glycinate

(+)ESI-MS m/z : 572, 574 $(M+H)^+$

(12) Sodium N-[[4-[4-[(2S)-3-hydroxy-2-[N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propyl]phenoxy]-8-quinolyl]carbonyl]-beta-alaninate

(+)ESI-MS m/z : 582 $(M+H)^+$

(13) Sodium N-[[4-[4-[(2S)-2-[N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]-carbonyl]-beta-alaninate

(+)ESI-MS m/z : 586, 588 $(M+H)^+$

Example 58

To a suspension of ethyl [[4-[4-[2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]-7-quinolyl]oxy]acetate dihydrochloride (35.0 mg) in ethanol (1.0 ml) was added 1N sodium hydroxide solution (237 μl) and the mixture was refluxed for 20 minutes. After cooling to room temperature, the solvent was removed by evaporation to give a white solid. The solid was acidified with 1N hydrochloric acid (500 μl) and the solvent was removed by evaporation. The residual solid was dissolved in hot water (500 μl) and the solution was stored at room temperature. The precipitates were collected by filtration, washed with a small portion of water, and dried under reduced pressure to give [[4-[4-[2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]-7-quinolyl]oxy]-acetic acid dihydrochloride (7.7 mg) as an off-white solid.
^{1}H NMR (200 MHz, DMSO-d_6): δ 3.11 (br, 6H), 4.00 (d, J=4.6Hz, 2H), 4.22 (br, 1H), 4.98 (s, 2H), 5.93 (br, 1H), 6.71 (d, J=6.1Hz, 1H), 6.93-7.00 (m, 3H), 7.32-7.38 (m, 4H), 7.48-7.57 (m, 4H), 8.40 (d, J=9.2Hz, 1H), 8.84 (d, J=6.1Hz, 1H)

Example 59

To a solution of tert-butyl [[4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]oxy]acetate (101 mg) in dichloromethane (1.0 ml) was added trifluoroacetic acid (200 μl) at room temperature. After stirring for 1 hour, the solvent was removed by evaporation. The residual yellow paste was dissolved in 4N hydrogen chloride in ethanol (5 ml) and the solution was stirred at room temperature for 3 days. The solvent was removed by evaporation and the residue was partitioned between ethyl acetate (20 ml) and a saturated solution of sodium hydrogencarbonate in water (20 ml). The organic layer was separated and washed with brine (20 ml×1), and then dried over magnesium sulfate. Filtration followed by evaporation gave a pale-yellow foam (90.8 mg). The crude product was purified by recycling preparative high pressure liquid chromatography equipped with a gel permeation chromatography column (chloroform) to give ethyl [[4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]oxy]acetate (72.5 mg) as a white foam.

MS m/z : 641 and 643 (MH^+)

Example 60

The following compounds were obtained in a manner similar to Example 59.

(1) Ethyl [[4-[4-[(2S)-2-[N-benzyl-N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolyl]oxy]-acetate

MS m/z : 637 (MH^+)

(2) Ethyl [N-[[4-[4-[(2S)-2-[N-benzyl-N-((2S)-2-hydroxy-3-phenoxypropyl)amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]-

carbonyl]amino]acetate
(+)APCI-MS m/z : 664 $(M+H)^+$

(3) Ethyl [N-[[4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]carbonyl]amino]acetate dihydrochloride
(+)APCI-MS m/z : 668, 670 $(M-2HCl+H)^+$

(4) Ethyl 3-[N-[[4-[4-[(2S)-2-[N-benzyl-N-((2S)-2-hydroxy-3-phenoxypropyl)amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]-carbonyl]amino]propanoate
(+)APCI-MS : 678 $(M+H)^+$

(5) Ethyl 3-[N-[[4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-8-quinolyl]carbonyl]amino]propanoate dihydrochloride
(+)ESI-MS m/z : 682, 684 $(M-2HCl+H)^+$

Example 61

The following compounds were obtained in a manner similar to Preparation 30.

(1) (2S)-3-[4-((7-Amino-4-quinolyl)oxy)phenyl]-2-[N-benzyl-N-((2S)-2-hydroxy-3-phenoxypropyl)amino]propan-1-ol
(+)ESI-MS m/z : 550 $(M+H)^+$

(2) (2S)-3-[4-[(7-Amino-4-quinolyl)oxy]phenyl]-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propan-1-ol
(+)APCI-MS m/z : 554, 556 $(M+H)^+$

Example 62

Under nitrogen at 5°C, to a solution of (2S)-3-[4-[(7-amino-4-quinolyl)oxy]phenyl]-2-[N-benzyl-N-((2S)-2-hydroxy-3-

phenoxypropyl)amino]propan-1-ol (500 mg) in dichloromethane (20 ml) was added N,O-bis(trimethylsilyl)acetamide (1.1 ml), and the mixture was stirred at room temperature for 30 minutes. After the mixture was cooled to 5°C, to this one was added ethyl chloroformate (0.44 ml), and the mixture was stirred at the same temperature for 1 hour. The mixture was poured into saturated aqueous sodium hydrogencarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform : methanol = 100 : 1 to 40 : 1). The obtained compound was dissolved in ethanol (5 ml) and to this one was added 1N hydrochloric acid. After stirring for 1 hour, the mixture was poured into saturated aqueous sodium hydrogencarbonate and the aqueous mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (chloroform : methanol = 100 : 1 to 30 : 1) to give ethyl 4-[4-[(2S)-2-[N-benzyl-N-((2S)-2-hydroxy-3-phenoxypropyl)amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarbamate (210 mg).

(+)APCI-MS m/z : 622 $(M+H)^+$

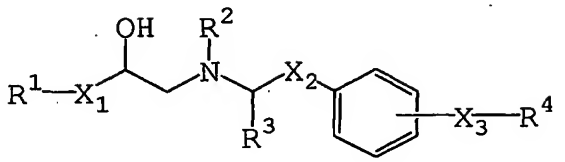
Example 63

Ethyl 4-[4-[(2S)-2-[N-benzyl-N-[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]-3-hydroxypropyl]phenoxy]-7-quinolinecarbamate was obtained in a manner similar to Example 62.

(+)ESI-MS m/z : 626, 628 $(M+H)^+$

CLAIMS

1. A compound of formula [I]:



[I]

wherein

X_1 is bond or $-OCH_2-$;

X_2 is $-(CH_2)_n-$, in which n is 1 or 2;

X_3 is bond, -O- or -NH-;

R^1 is phenyl, indolyl or carbazolyl, each of which is optionally substituted with one or two substituent(s) selected from the group consisting of hydroxy, halogen, nitro, amino, formyl, (lower)alkylsulfonylamino, aryl(lower)alkoxy and hydroxy(lower)alkyl;

R^2 is hydrogen or aryl(lower)alkyl;

R^3 is hydrogen or hydroxy(lower)alkyl;

R^4 is aryl, 4-quinolyl, phthalazinyl, quinazolinyl, cinnolinyl or naphthyridinyl, each of which is optionally substituted with one or two substituent(s) selected from the group consisting of fluoro, carboxy, nitro, amino, halo(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxycarbonyl, (lower)alkylsulfonylcarbamoyl optionally substituted with cyclo(lower)alkyl or halogen atom(s) in which amine hydrogen is optionally substituted with lower alkyl, cyclo(lower)alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, (lower)alkylcarbonylamino in which amine hydrogen is optionally substituted with lower alkyl, lower alkoxy optionally substituted with carboxy or (lower)alkoxycarbonyl,

(lower)alkylsulfonylamino in which amine hydrogen is optionally substituted with lower alkyl,
ureido in which amine hydrogen(s) is(are) optionally substituted with lower alkyl,
(lower)alkoxycarbonylamino in which amine hydrogen is optionally substituted with lower alkyl, and

$-CONR^5R^6$

(wherein R^5 and R^6 are independently hydrogen or lower alkyl optionally substituted with hydroxy, carboxy, lower alkoxy, (lower)alkoxycarbonyl or halogen atom(s), or R^5 and R^6 together can be four or five methylene groups, of which one methylene group can be replaced by O, N-H or N-(lower)alkyl), and a salt thereof,
provided that
(1) when R^4 is unsubstituted 4-quinolyl, X_2 is $-(CH_2)_2-$,
(2) when R^4 is 4-quinolyl substituted with one substituent which is ethoxycarbonyl, carboxy, carbamoyl or methoxy substituted at the 7-position thereof, X_1 is a bond,
(3) when R^4 is 4-quinolyl substituted with fluorine, it is substituted at the 2-, 3-, 5-, 7- or 8-position thereof,
(4) when R^4 is aryl optionally substituted with halogen, X_3 is bond or -NH-, and
(5) when R^4 is naphthyridinyl, it is substituted with the above-mentioned one or two substituent(s).

2. A compound of claim 1, wherein
X_1 is $-OCH_2-$;
X_2 is $-CH_2-$;
X_3 is -O-;
R^1 is phenyl optionally substituted with one or two substituent(s) selected from the group consisting of hydroxy,

halogen, nitro, amino, formyl, (lower)alkylsulfonylamino, aryl(lower)alkoxy and hydroxy(lower)alkyl;

R^2 is hydrogen; and

R^3 is hydroxy(lower)alkyl.

3. A compound of claim 2, wherein

R^4 is 4-quinolyl optionally substituted with one or two substituent(s) selected from the group consisting of fluoro, carboxy, nitro, amino, halo(lower)alkyl, hydroxy(lower)alkyl, (lower)alkoxycarbonyl,
(lower)alkylsulfonylcarbamoyl optionally substituted with cyclo(lower)alkyl or halogen atom(s) in which amine hydrogen is optionally substituted with lower alkyl,
cyclo(lower)alkylsulfonylcarbamoyl,
arylsulfonylcarbamoyl,
(lower)alkylcarbonylamino in which amine hydrogen is optionally substituted with lower alkyl,
lower alkoxy optionally substituted with carboxy or (lower)alkoxycarbonyl,
(lower)alkylsulfonylamino in which amine hydrogen is optionally substituted with lower alkyl,
ureido in which amine hydrogen(s) is (are) optionally substituted with lower alkyl,
(lower)alkoxycarbonylamino in which amine hydrogen is optionally substituted with lower alkyl, and

$-CONR^5R^6$

(wherein R^5 and R^6 are independently hydrogen or lower alkyl optionally substituted with hydroxy, carboxy, lower alkoxy, (lower)alkoxycarbonyl or halogen atom(s), or R^5 and R^6 together can be four or five methylene groups, of which one methylene group can be replaced by O, N-H or N-(lower)alkyl).

4. A compound of claim 3, which is selected from a group which consists of

(1) N-[[4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-1-propanesulfonamide,

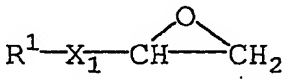
(2) N-[[4-[4-[(2S)-3-Hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-7-quinolyl]carbonyl]-beta-alanine, and

(3) N-(2-Hydroxyethyl)-4-[4-[(2S)-3-hydroxy-2-[N-[(2S)-2-hydroxy-3-phenoxypropyl]amino]propyl]phenoxy]-8-quinolinecarboxamide,

or a pharmaceutically acceptable salt thereof.

5. A process for preparing a compound of claim 1, or a salt thereof, which comprises,

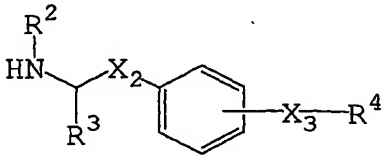
(i) reacting a compound [II] of the formula:



[II]

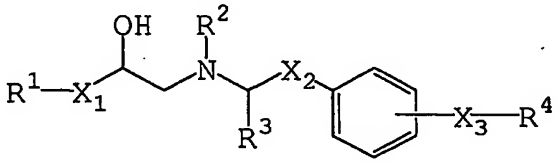
wherein X_1 and R^1 are each as defined in claim 1, or a salt thereof

with a compound [III] of the formula:



[III]

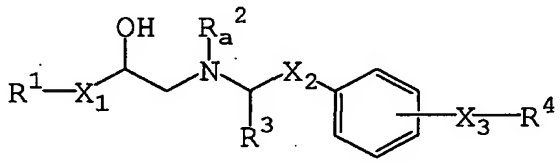
wherein X_2, X_3, R^2, R^3 and R^4 are each as defined in claim 1, or a salt thereof, to give a compound [I] of the formula:



[I]

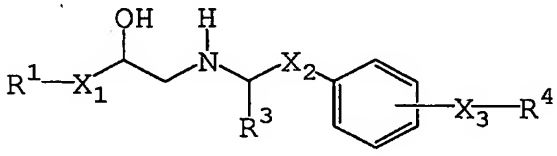
wherein X_1, X_2, X_3, R^1, R^2, R^3 and R^4 are each as defined in claim 1, or a salt thereof,

(ii) subjecting a compound [Ia] of the formula:



[Ia]

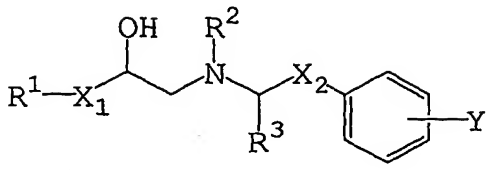
wherein X_1, X_2, X_3, R^1, R^3 and R^4 are each as defined in claim 1, and R^2_a is amino protective group, or a salt thereof, to elimination reaction of the amino protective group, to give a compound [Ib] of the formula:



[Ib]

wherein X_1, X_2, X_3, R^1, R^3 and R^4 are each as defined in claim 1, or a salt thereof, or

(iii) reacting a compound [IV] of the formula:

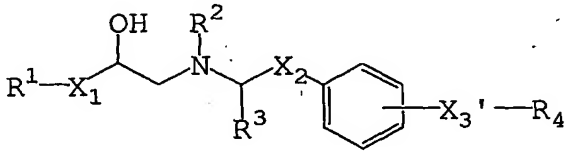


[IV]

wherein X_1, X_2, R^1, R^2 and R^3 are each as defined in claim 1 and Y is hydroxy or amino, or a salt thereof,
with a compound [V] of the formula:

[V]

wherein R^4 is as defined in claim 1, and X is halogen, or a salt thereof to give a compound [Ic] of the formula:



[Ic]

wherein X_1, X_2, R^1, R^2, R^3 and R^4 are each as defined in claim 1 and X_3' is -O- or -NH-, or a salt thereof.

6. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers or excipients.

7. Use of compound of claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament.

8. A compound of claim 1 or pharmaceutically acceptable

salt thereof for the manufacture of a medicament.

9. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as selective β_3 adrenergic receptor agonists.

10. A method for the prophylactic and/or the therapeutic treatment of pollakiurea or urinary incontinence which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.

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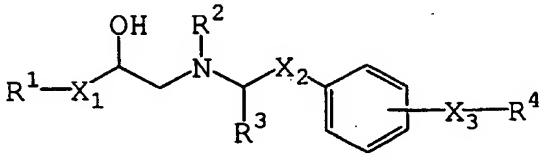
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AMINOALCOHOL DERIVATIVES



(I)

(57) Abstract: The present invention relates to a compound of formula (I): wherein X_1 is bond or $-OCH_2-$; X_2 is $-(CH_2)_n-$, in which n is 1 or 2; X_3 is bond, -O- or -NH-; R^1 is phenyl, indolyl or carbazolyl, each of which is optionally substituted with one or two substituent(s) selected from the group consisting of hydroxy, halogen, nitro, amino, formyl, (lower)alkylsulfonylamino, aryl(lower)alkoxy and hydroxy(lower)alkyl; R^2 is hydrogen or aryl(lower)alkyl; R^3 is hydrogen or hydroxy(lower)alkyl; R^4 is aryl, 4-quinolyl, phthalazinyl, quinazolinyl, cinnolinyl or naphthyridinyl, each of which is optionally substituted with one or two substituent(s) defined in the specification, or a salt thereof. The compound (I) of the present invention and pharmaceutically acceptable salts thereof are useful for the prophylactic and/or the therapeutic treatment of pollakiurea or urinary incontinence.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 01/05425

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	column 10, line 29-31	1-9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 May 2002	10/06/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoepfner, W

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 01/05425

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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